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THE MAYO CLINIC
and
THE MAYO FOUNDATION

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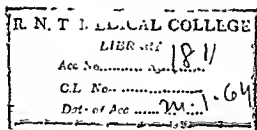
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FOREWORD

Volumes of this series are prepared primarily for the general practitioner, the general surgeon and the diagnostician. To represent adequately the work of the Mayo Clinic and the Mayo Foundation, however, for some years the specialties and pure science have required representation.

For reasons that have been given in previous volumes, only the titles of articles which have been published in Mayo Clinic numbers of Medical Clinics of North America and of Surgical Clinics of North America are printed herein. Also explained before are the principles which guide the editors in choosing articles from the Proceedings of the Staff Meetings of the Mayo Clinic for representation in this book.

Material represented herein was received from December 1, 1946 to November 30, 1947, inclusive. It was composed of 751 papers, 122 of them from the Proceedings. Of these seventy appear in full, sixty-six by abridgment, eighty-six by abstract and of 529, the titles only are given.

On the title page the names of the editors appear. Equally essential work, however, was done by the following: Marcia Nutting, executive assistant, and her aids Bereith Bandel Lemon, Irene Weist Southwick and Bernette Himle; Eleanore Clappier, managing editor of the Proceedings and her assistants Helen Taylor Beahrs and Margaret Thompson; Beryl Davis, Alice Cartwright, Dorothy Willis and Mary Ann Grottum, who read the proof.

ROCHESTER, MINNESOTA
November, 1948

DIVISION OF PUBLICATIONS,
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AND
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ALIMENTARY TRACT

ESOPHAGEAL HIATAL HERNIAS OF THE SHORT ESOPHAGUS TYPE: ETIOLOGIC AND THERAPEUTIC CONSIDERATIONS*

ARTHUR M. OLSEN AND STUART W. HARRINGTON

Herniation of the stomach through the esophageal hiatus of the diaphragm has been a subject of great interest in recent years. Improvements in roentgenographic methods have enabled the roentgenologist to recognize this condition with increasing frequency. Although the clinician has become conscious of the frequent occurrence of hiatal hernia and is familiar with the symptom complex which suggests this condition, it remains for the roentgenologist actually to demonstrate the presence of hernia.

The present paper concerns our experience in 220 cases of short esophagus with partial thoracic stomach that have been seen at the Mayo Clinic in the past eleven years (1935 through 1945). As will be readily apparent, hernia of the short esophagus type presents problems different from those of the usual hiatal hernia. It is of interest that the cases of short esophagus comprise approximately 10 per cent of the total number of hiatal hernias seen in this period.

PRESENTATION OF DATA

The diagnosis of short esophagus with partial thoracic stomach was made on the basis of roentgenographic findings, esophagoscopic examination and, in many cases, histologic study of tissue removed at esophagoscopic examination. In many instances the roentgenologic evidence of short esophagus with partial thoracic stomach was indisputable. In 149 of the 220 cases (68 per cent), the diagnosis was confirmed or established by esophagoscopic examination. Difficulty in the differential diagnosis between stricture of the esophagus with and without a partial thoracic stomach was encountered in some cases. In questionable cases, biopsy of the mucosa just below the stricture was taken at esophagoscopic examination for identification of the mucosa. In fifty-two cases of such character, gastric mucosa was recognized at histologic examination. All cases of esophageal stricture of doubtful etiology were excluded from the group.

AGE, SEX AND OBESITY

Of the 220 patients, 141 (64 per cent) were males and seventy-nine (36 per cent) were females. The age of the patients is indicated in figure 1. The great majority of patients were in the older age group. In this entire series, 115 patients (52 per cent) were obese at the time of examination or

* Abridgment of paper published in full in *The Journal of Thoracic Surgery*, 17:189-209 (Apr.) 1948.

had been obese prior to the development of symptoms of obstruction. On the other hand twenty-four (11 per cent) were greatly undernourished. These latter also had esophageal obstruction.

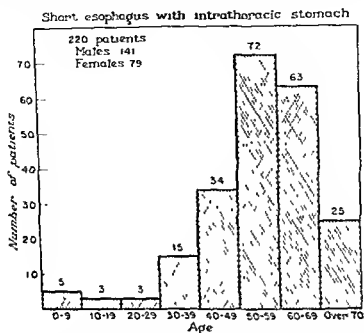


Fig 1 — Age distribution in cases of short esophagus with partial intrathoracic stomach.

SYMPTOMS

The symptoms arising from the esophagus are particularly significant in cases of short esophagus and have been tabulated in the 220 cases studied in this series (table 1).

TABLE 1
SYMPTOMS REFERABLE TO ESOPHAGUS IN 220 CASES IN SERIES*

	Cases	
	Number	Per cent
Obstruction to swallowing . . .	165	75
Substernal distress . . .	71	32
Esophageal pain	20	9
Hemorrhage	19	8
No esophageal symptoms . . .	17	8

* More than one symptom in many cases.

The frequent occurrence of dysphagia is noteworthy. One hundred sixty five of the 220 patients (75 per cent) complained of obstruction to the passage of food on swallowing. In 154 of these cases, an actual obstruction was demonstrated, either at esophagoscopy examination or when sounds were passed over a previously swallowed thread. It is of interest that in seventy-six cases, the dysphagia was intermittent or the symptoms of obstruction varied in degree. This observation certainly indicates that spasm of the esophagus plays a definite part in the dysphagia associated with the short esophagus in many cases.

ROENTGENOLOGIC DIAGNOSIS

The roentgenoscopic diagnoses in our 220 cases are listed in table 2. In 182 of these cases the amount of stomach above the diaphragm was estimated. In 35 per cent there were 2 inches (5 cm.) or less of stomach above

TABLE 2

ROENTGENOSCOPIC DIAGNOSIS IN CASES OF SHORT ESOPHAGUS
1933 THROUGH 1946

	Cases
Short esophagus	135
Hiatal hernia	46*
Stricture of lower part of esophagus	30
Esophageal spasm	7
Carcinoma (associated with hernia)	3
Indeterminate	1
Total	220

* In the early years covered by this investigation no effort was made to determine the type of hernia.

the diaphragm. From 2 to 4 inches (5 to 10 cm.) of stomach were visible above the hiatus in 53 per cent, and more than 4 inches (10 cm.) of stomach were intrathoracic in 12 per cent.

ESOPHACOSCOPIC FINDINGS

Esophagoscopy was performed in 149 (68 per cent) of the 220 cases. Examinations were performed once in 125, twice in eighteen, three times in four, and four times in two cases. In 126 of the 149 cases in which esophagoscopy was carried out, the distance from the upper incisor teeth to the esophagogastric junction was measured at the time of esophagoscopy. This distance was 14 inches (35.6 cm.) or more in 36 per cent, and less than 14 inches in 64 per cent of cases. Inasmuch as the distance from the upper incisor teeth to the esophagogastric junction at the diaphragm is approximately 16 inches (40.6 cm.) in the average normal adult, it is evident that the esophagoscopist and the roentgenologist agreed closely in their estimations of the amount of stomach in the thorax.

The presence or absence of ulceration was noted in all cases. Significant ulceration was reported in eighty-nine cases (60 per cent), slight ulceration in twelve cases (8 per cent) and no ulceration in forty-seven cases (32 per cent). At the time of esophagoscopy evidence of diffuse ulcerative esophagitis was found in twenty-two cases (15 per cent).

Specimens of tissue were taken for microscopic examination in eighty-six cases. In many cases esophageal stricture was present and tissue was removed in order to determine the type of mucosa immediately below the obstruction. In fifty-two cases gastric mucosa was demonstrated at histologic examination to prove that a short esophagus was present. In thirty-four cases biopsy was carried out to exclude malignant disease. In three cases carcinoma was found in association with a short esophagus and partial thoracic stomach. Two of these carcinomas were gastric in origin; the other was a squamous cell lesion. In thirty-one cases inflammatory tissue was obtained. Adenocarcinoma occurring in the herniated portion of the stomach was revealed at transthoracic exploratory operation in one additional case in the series.

In our experience, esophagoscopy examinations are performed most satisfactorily with the aid of both topical and general anesthesia. After the throat is prepared by topical application of a solution of 20 per cent cocaine to the piriform sinuses, the patient is anesthetized with pentothal sodium, administered intravenously. In a patient who has a short esophagus, the esophagus is found to be a straight tube without tortuosity or redundancy. The normal deviation of the lower part of the esophagus anteriorly and to the left is absent. If organic stenosis is not present, the esophagogastric junction is usually found to be open; the normal sphincteric action of the cardia is not encountered, and there is often a free flow of gastric secretions into the esophagus (incompetent cardiac sphincter). Shortness of the esophagus may be demonstrated by actual measurement also.

ETIOLOGY OF THE SHORT ESOPHAGUS

Congenital Short Esophagus.—The 220 cases of short esophagus which are the basis of this report were studied carefully from the standpoint of etiology. Patients who gave a history of dysphagia from birth or early childhood were considered to have a true "congenital short esophagus." There were nine (4 per cent) such patients. Their ages varied from three to thirty-six years. Five of them were less than ten years of age at the time they were first seen at the clinic, two were between ten and nineteen years of age, and two patients were thirty-five and thirty-six years of age, respectively. None of these patients gave any history of ingestion of lye or other caustic poisons. All nine had smooth strictures at the esophagogastric juncture without evidence of ulceration. All were treated successfully at the clinic or elsewhere by means of dilatations performed over previously swallowed threads (fig. 2).

Why all the patients who had true congenital shortening of the esophagus had associated strictures is a question that is difficult to answer. These cases are similar to the series reported by Findlay and Kelly and Manges and Clerf. Obviously, the presence of esophageal stenosis permitted an early recognition of the condition and it is conceivable that true congenital shortening of the esophagus has escaped detection in other cases because of the absence of any symptoms.

Short Esophagus of Indeterminate Etiology.—The next group of patients to be considered are those who presented the picture of short esophagus without any obvious etiologic basis. There were forty patients (18 per cent) with shortening of the esophagus of indeterminate etiology. Five of

these forty patients, all between forty-five and sixty years of age, had no symptoms referable to the gastro-intestinal tract. Roentgenologic studies of the esophagus and stomach had been performed at the patients' request. Although no endoscopic studies were done on these five patients, the roentgenologist's diagnosis of short esophagus was definite. The other thirty-five patients in the group in which the etiology was indeterminate came to the clinic complaining of difficulty in swallowing of recent origin but had no other symptoms or history of digestive difficulty (fig. 3). We do not believe that these patients had true congenital short esophagus.

Although the etiologic factor in the cases in this group has been labeled as "indeterminate," it is conceivable that a combination of hiatus insuf-

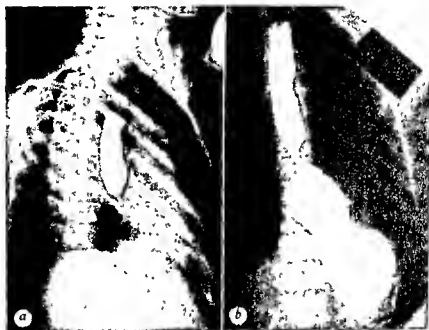


Fig 2—Congenital short esophagus with stricture in a boy aged six years in 1932 who had had dysphagia since birth. Symptoms have been controlled by dilatation since 1932; a, esophagus and stomach in 1932; b, in 1945.

iciency, atrophy of the diaphragmatico-esophageal membrane, spasm of the esophagus, incompetence of the cardiac sphincter and finally ulcerative esophagitis may have produced the end result. The patients probably had esophageal hiatal hernia of long standing which produced few or no symptoms until cicatrization of the lower part of the esophagus gave obstructive symptoms.

Acquired Short Esophagus.—Of the 220 cases of short esophagus with partial thoracic stomach, there was an apparent etiologic factor in 171 (78 per cent). These cases may be divided into several groups. In the first group the patients gave a history of excessive vomiting. Of the thirty-six patients in this group, nineteen had obstructive duodenal ulcers, seven had vomiting associated with various surgical conditions, two had vomiting

of pregnancy, one vomited because of a brain tumor, one had frequent bouts of migraine with vomiting, and six vomited as part of a syndrome of dyspepsia or gallbladder disease. In this group, the stenosis of the lower part of the esophagus was often pronounced and a number of these patients came to us with almost complete esophageal obstruction.

In the second group of acquired short esophagus there were sixty-three cases. These patients gave histories and had signs which suggested that an esophageal hiatal hernia of the para-esophageal or sliding type had been



Fig 3—Hiatal hernia of short esophagus type of indeterminate etiology in a woman aged forty-five years who had had dysphagia for three years without other symptoms. Esophagoscopy revealed a smooth stricture with foreign body (kernel of corn). Dilatations to the size of a 45 F. and were done on two occasions two years apart.

resent for a considerable time. Characteristically, these patients had experienced epigastric and substernal distress which was made worse by lying down. In this group of cases, it was felt that esophagitis and recurring ulceration of the lower part of the esophagus had resulted in cicatrization and shortening of the esophagus (fig. 4). Seventeen of these sixty-three patients had had operations for repair of hiatal hernia. In these seventeen patients, temporary interruption of the left phrenic nerve was followed by abdominal operation with replacement of the herniated stomach into the abdomen. In some of these cases shortening of the esophagus was noted at

operation. In others shortening apparently took place as a result of esophagitis after operation. The operative cases will be discussed later under treatment.

It is of interest that twenty-three of the 220 patients in our series had gallbladder disease, in addition to the short esophagus with partial thoracic stomach. Also, thirty-two patients gave a history of significant surgical procedures on the upper part of the abdomen exclusive of repair of hiatal hernia.



Fig. 4.—Hiatal hernia of short esophagus type in a woman aged sixty-one years. Diagnosis of large esophageal hiatal hernia had been made ten years previously. Dysphagia present one year only. At esophagoscopy marked esophagitis and ulceration present. Stricture and gastric mucous membrane 19½ inches (31.8 cm.) from margin of the upper teeth. Relief of dysphagia by dilatation.

In fifty-seven cases the patients gave a history of upper abdominal distress of long duration. Eighteen of these patients had duodenal ulcers without evidence of pyloric obstruction. The remainder had epigastric distress which was not suggestive of esophageal hiatal hernia.

In nine patients in this series a short esophagus with partial thoracic stomach was associated with scleroderma (acrosclerosis). The esophageal lesions of scleroderma have been reported by O'Leary, Kirklin and one of us (A. M. O.). Involvement of the esophageal wall by the sclerodermatous process is apparently responsible for the shortening of the esophagus in this group.

In two cases the short esophagus apparently developed secondary to cardiospasm. One of these patients, a man fifty-seven years of age, had had dysphagia for twenty-four years. He was seen periodically at the clinic for twelve years before roentgenologic evidence of shortening of the esophagus developed. The other patient, a woman sixty-one years of age, had both cardiospasm and hiatal hernia in 1941 and on her return in 1944 was found to have a short esophagus.

Four patients were seen who had carcinoma associated with short esophagus. In three of these patients the carcinoma was gastric in origin. The fourth patient had a squamous cell carcinoma.

Comment.—As has been pointed out previously by one of us (S. W. H.), the evidence indicates that true congenital short esophagus is rare. It occurred in 4 per cent of our group. The congenital factor which appears to play a part in the development of all hiatal hernias is congenital enlargement of the esophageal hiatus of the diaphragm. Weakening or disruption of the diaphragmatico-esophageal membrane is also necessary for the development of hernia. Atrophy of this membrane apparently occurs in older persons. Increased intra-abdominal pressure, especially that associated with obesity, plays a part in the development of hiatal hernias.

It is reasonably well established that the short esophagus may be caused by severe esophagitis and ulceration of the lower part of the esophagus followed by healing and cicatrization. This is best illustrated by cases of excessive vomiting, in which shortening of the esophagus resulted. Acid gastric secretions undoubtedly produced "peptic" ulceration of the lower part of the esophagus. Yet we have reason to believe that cardio-esophageal relaxation alone (incompetence of the physiologic sphincter at the cardia permitting regurgitation of acid secretions into the esophagus) is probably not sufficient in itself to cause esophagitis or ulceration. However, if incompetence of the cardiac sphincter is associated with hiatal insufficiency or hiatal hernia over a long period, ulceration of the lower part of the esophagus with shortening may occur.

Furthermore, reflex spasm of the esophagus appears to play a part in producing hiatal hernia and short esophagus. Inasmuch as this reflex spasm may be produced experimentally by vagal stimulation or manipulation of upper abdominal organs, it is reasonable to assume that disorders of the upper part of the abdomen should cause this spasm clinically. The correlation of short esophagus with digestive disturbances in our series should add weight to this reasoning. It is probable that reflex spasm and shortening of the esophagus is the first stage in the development of the short esophagus.

TREATMENT

Patients with hiatal hernias of the short esophagus type are not good candidates for radical surgical repair. Results are not nearly as satisfactory as in those cases in which the esophagus is normal in length. Even though it may be possible to replace the stomach below the diaphragm after temporary interruption of the left phrenic nerve, recurrences are common in the short esophagus group. As a rule it is desirable to treat these patients by medical means.

In certain cases, however, surgical treatment of the short esophagus may be indicated. In some cases symptoms are so severe that some type of

surgical treatment must be considered. In four patients in our group, temporary or permanent interruption of the left phrenic nerve only was carried out. Three of these four patients were benefited by this procedure; one of them had had severe hemorrhages which did not recur after phrenicotomy.

Seventeen patients in this group underwent surgical repair (table 3). Abdominal operations were performed, the herniated stomach was replaced, the hernial sac was removed, and the abnormally enlarged esophageal hiatus was repaired. In some cases of short esophagus the surgical problem is that of reconstruction and elevation of the diaphragm to a position above the stomach. In most of our seventeen cases, shortening of the esophagus was noted at the time of operation or had been known prior to operation. In some of the cases, however, progressive esophagitis resulted in shortening of the esophagus after an apparent successful repair.

The most common symptom demanding treatment in the 220 cases was dysphagia. In our experience dysphagia has been treated most satisfactorily by dilatations performed over a previously swallowed thread. In patients whose dysphagia is caused by spasm, dilatation with a 50 F. sound can be accomplished with ease. However, in the great majority of instances,

TABLE 3

TREATMENT

Treatment	Cases
Interruption of phrenic nerve and surgical repair	17
Interruption of phrenic nerve only	4
Dilatation of stricture	145
Dilated once.	79
Dilated twice..	23
Dilated three times.....	14
Dilated four times or more	29

organic stenosis is present and graduated sounds up to 45 F. must be used. Because of the cicatricial nature of the stenosis, dilatation must be repeated from time to time. Dilatations were performed in 145 of our 220 cases (table 3). In about half of these only one series of dilatations was carried out at the clinic. In some of the cases twenty or thirty dilatations were necessary in a period of years.

In the early phases of treatment of patients with organic stenosis, dilatations must be carried out every few weeks. However, it usually is possible to increase the intervals between dilatations up to six months or more.

On the whole, the results of treating these strictures with dilating sounds have been satisfactory. Most of the patients are able to eat almost normally. The risk of performing dilatations in this group of cases by the method described is small. We have had no fatalities resulting from dilatation in these cases. Dilatation should never be done by blind bougienage.

Medical treatment is directed against the further development of ulceration in the esophagus. In the presence of ulcerative esophagitis, a bland type of diet such as that employed in peptic ulcer is desirable. The frequent use of antacid preparations will keep gastric secretions neutralized. For patients

who are overweight a reduction program is imperative. It is amazing how often symptoms of hiatal hernia can be controlled by keeping the weight down and reducing the intra-abdominal pressure. Elevation of the head of the patient's bed is a valuable aid. The head of the bed should be raised 12 to 15 inches (30 to 38 cm.) above the foot. This procedure tends to prevent regurgitation of secretions into the esophagus during the night.

Admittedly, the management of short esophagus with a partial thoracic stomach is not as satisfactory as the surgical repair of the other types of diaphragmatic hernia. However, the majority of patients who have a short esophagus can live comfortably if they will follow the regimen outlined and report for dilatations when necessary.

SUMMARY

A study of 220 cases of short esophagus with partial thoracic stomach was made. On the basis of this review, the following conclusions may be drawn and observations made:

True congenital short esophagus is rare (4 per cent of the cases in our series). In an overwhelming majority of the cases shortening of the esophagus is acquired in later years of the patient's life.

Basic anatomic factors in the development of hiatal hernia are congenital enlargement of the esophageal hiatus of the diaphragm and atrophy or weakness of the diaphragmatico-esophageal membrane.

Shortening of the esophagus develops as a result of "peptic" ulceration of the esophagus. Peptic ulceration of the esophagus may be the result of (1) excessive or prolonged vomiting, or (2) incompetence of the physiologic sphincter at the cardia, when it occurs in association with hiatal hernia or with reflex spasm of the lower part of the esophagus. Reflex spasm of the esophagus is the result of stimulation of the vagus nerve and may be produced by a variety of digestive disorders.

Dysphagia is the most common symptom associated with the short esophagus. In early stages, spasm may be the cause of dysphagia. However, organic stenosis of the lower part of the esophagus develops in most cases.

Hiatal hernia of the short esophagus type is not favorable for surgical treatment. When dysphagia is present, dilatation may be carried out by passing sounds over a previously swallowed thread. Medical measures are directed against further ulceration of the lower part of the esophagus.

Because the treatment of short esophagus type of hernia is radically different from that of the usual hiatal hernia, it is important that an accurate diagnosis be made. Careful roentgenoscopic studies are necessary and esophagoscopy examination is frequently required if hiatal hernias of the short esophagus type are to be differentiated from hiatal hernias with esophagus of normal length.

FAVORABLE AND UNFAVORABLE RESULTS OF RESECTION OF THE VAGUS NERVES FOR PEPTIC ULCER*

WALTMAN WALTERS AND HAROLD A. NEIBLING

Last year in speaking before the meeting of the Interstate Postgraduate Medical Association one of us (W. W.) considered some of the recent advances in the management of surgical lesions of the upper part of the abdomen. At that time also rather brief reference was made to experience with resection of the vagus nerves or vagotomy in twenty-one cases of peptic ulceration. Operations in these twenty-one cases had been performed in the preceding eight months. In one of these cases a large recurring perforating gastric ulcer had developed after complete vagotomy and had produced symptoms which necessitated its removal by partial gastrectomy (case 1, table 1).

TABLE 1
DEFINITE RECURRENCE OF ULCER AFTER VAGOTOMY

Case	Ulcer and time of vagotomy	Associated operation	Result of anakin test	Postoperative symptoms	Postoperative roentgenologic diagnosis and date	Treatment
1	Gastric ulcer 7-22-46	Excision of ulcer	Negative	Ulcer distress	Penetrating gastric ulcer 11-18-46	Medical management unsuccessful, high gastric resection 7-15-47 for penetrating gastric ulcer
2	Duodenal ulcer 2-26-46	Anterior gastro-enterostomy with subsequent jejunojejunostomy	Negative	Atypical ulcer distress	Negative, gastroscopic positive for ulcer 2-1-47	Closure of gastro-enteric stoma, resection of stomach 3-15-47 for anterior penetrating gastrojejunal ulcer
3	Gastro-jejunal ulcer 10-14-46	Removal of gastro-enteric stoma, excision of ulcer and pyloroplasty	Negative	Poor appetite, moderate distress	Duodenal ulcer with crater 8-27-47	Medical management

UNFAVORABLE RESULTS

Since that time recurring perforating craterous peptic ulcers have followed complete vagotomy or resection of the vagus nerves in two additional cases in our series (cases 2 and 3, table 1). This operation was performed in association with anterior gastro-enterostomy and jejunojejunostomy in one case and with excision of the gastrojejunal ulcer, disconnection of the gastro-enteric anastomosis and pyloroplasty in the other. In the former case pain necessitated a second operation on August 15, 1947. A recurring anastomotic ulcer perforating into the abdominal wall was found and partial gastrectomy was carried out. The other patient who underwent resection of the vagus nerves on October 14, 1946, returned at our request for re-examination on August 24, 1947, at which time there was roentgenographic evidence of a recurring perforating duodenal ulcer with crater. The insulin

* From Postgraduate Medicine. 4 6-11 (July) 1948.

test on August 26, 1947, gave negative results. In both of these cases the results of the Hollander insulin tests were negative which, according to Dragstedt, is indicative of complete severance of the vagus nerves of the stomach.

In another case roentgenographic evidence of jejunitis was found four weeks subsequent to operation. This patient, however, did not have any recurrence of the ulcer symptoms which were severe before operation. The insulin test on this patient, likewise, gave negative results.

Three additional patients in our series (table 2) continued to have distress of ulcer type for nine to ten months following their operations. Results of insulin tests on two were negative and no insulin test had been done on the third. Roentgenographic studies on one did not give any evidence of ulceration and postoperative roentgenologic examinations were not made on the other two.

The proved incidence of recurring ulceration, therefore, is 6 per cent in the fifty cases in which one of us (W. W.) carried out resection of the vagus

TABLE 2

SUSPECTED RECURRENCES OF ULCER NOT CONFIRMED BY ROENTGENOLOGIC EXAMINATION

Case	Type of ulcer and date of vagotomy	Associated operation	Result of insulin test	Postoperative symptoms
4	Duodenal ulcer 10/31/46	Posterior gastro-enterostomy	Negative	Ulcer distress; fullness; vomiting; loss of weight
5	Gastric ulcer and gastritis 9/27/46	Gastrotomy	Negative	Ulcer distress gradually diminishing; occasional vomiting
6	Duodenal ulcer 6/6/46	Anterior gastro-enterostomy	None	Ulcer distress

nerves in the period from March, 1946, to March 1, 1947, and symptoms of ulcer persisted in another 6 per cent.

The question has been raised whether the technic of the transabdominal resection of vagus nerves, which was used in these cases and in others which we have reported, has resulted in complete vagotomy. The answer is: if the Hollander insulin test is an indication of the completeness with which the vagus nerves in the stomach are resected, then complete vagotomy was accomplished in all three cases of proved recurring ulceration and in two of the three cases in which the symptoms of ulcer persisted, for, in all five cases results of insulin tests were negative. Moreover, the exposure of the lower part of the esophagus and the vagus nerves, which was obtained during the course of the operation of transabdominal resection of the vagus nerves was good as was indicated by the motion picture which followed this presentation at the meeting.

Unfortunately recurring ulceration is not the only serious complication which follows the operation, for in studying the effects of the operation

on the motility of the gastro-intestinal tract, nine months after operation, we have found that 12 per cent of the patients have had persistent, troublesome symptoms, such as bloating, belching of foul-smelling gas, loss of appetite, and sometimes vomiting or diarrhea, a series of complications which have been most difficult to control. Some of these patients have complained bitterly of these symptoms. It was our hope that administration of urethane of β -methylcholine chloride (urecholine) as a parasympathetic stimulant would be helpful in relieving the discomfort since Ruffin, Grimson and Smith have shown that it will increase the frequency and amplitude of waves of gastric peristalsis. Recently four of our patients who have severe early postoperative disturbance of motility received no benefit from the use of urethane of β -methylcholine chloride. In all, results of insulin tests were negative. Our experience with this preparation in relieving the distress of the vagotomized atonic stomach has been disappointing.

That the operation is not without an immediate and possibly a future risk cannot be denied even though that risk is small. In one of our colleagues' cases in which resection of the vagus nerves and posterior gastro-enterostomy were performed simultaneously in the treatment of a duodenal ulcer, persistent gastric retention with hypoproteinemia occurred. In spite of all efforts directed toward control of these factors the patient died on the fourteenth day after operation. At necropsy an unsuspected subdiaphragmatic abscess, the result of perforation of the duodenal ulcer, was found. Resection of the vagus nerves apparently masked the symptoms of perforation in this case and may have done so in two of our cases in which recurring ulcers developed. In one of these cases pain occurred in the lower anterior portion of the thorax and the left upper part of the abdomen on motion, which probably was the result of the perforation of the gastrojejunal ulcer with its base on the abdominal wall. Moreover, in this case relief of distress by food and soda was not the same as that frequently noted in the presence of perforating gastrojejunal ulcer when vagotomy had not been performed. The other patient has had no pain typical of ulcer but has lost his appetite during the past three months (seven months after vagotomy, disconnection of the gastro-enteric anastomosis, excision of a gastrojejunal ulcer and pyloroplasty). The roentgenogram shows a recurring duodenal ulcer with a crater.

In speculating on causes of relief of pain referable to the ulcer immediately following vagotomy, we have called attention previously to the fact that the relief of pain was not due to the healing of the ulcer, first, because it could not heal in such a short time but also because, in four of our cases in which pain was relieved, roentgenographic examination from two and a half to three weeks following operation revealed persistence of the peptic ulceration.

During the first three months' period (March, April and May, 1946) in which one of us (W. W.) was performing transabdominal vagotomy, we were a little reluctant to accept the risk incurred in reducing the patient's blood sugar level to 40 mg. per 100 c.c. or less by injections of insulin in order to determine whether the volume of gastric acids would increase. If increase occurs, the result of the test is considered positive and a positive reaction indicates that all of the branches of the vagus nerves to the stomach had not been cut. After the problem was discussed with one of our surgical

friends from another clinic, who assured us that he had carried out the procedure in many cases without risk, we began using it as a routine procedure approximately ten to fourteen days after vagotomy if the patient's general condition permitted. Therefore, from that time on we have obtained insulin tests in thirty-nine out of forty cases. A study of these insulin tests discloses that in 67 per cent of the cases negative results were obtained. These negative results indicate that all branches of the vagus nerves to the stomach had been resected. In 33 per cent of the forty cases, however, the tests gave positive results. In both groups we have studied the response to resection of the vagus nerves alone and in combination with other operations on the stomach with regard to (1) relief of symptoms of ulcer, (2) reduction of gastric acidity and (3) the incidence of motility disturbances producing troublesome symptoms. In the cases in which results of the insulin tests were positive, a greater reduction of gastric acidity occurred and achlorhydria developed in a greater percentage than in the cases in which insulin tests were negative. These figures were 93 per cent and 69 per cent, respectively. The incidence of troublesome disturbances of motility were about equal in the two groups. The most striking observation, however, is the fact that all recurrences of ulceration took place in the group of cases in which the results of insulin tests were negative, a circumstance which we are unable to explain.

In trying to explain the difference in these results with those reported by Dragstedt and his associates, we have compared the relative incidence in which the operation was performed for duodenal ulcer, gastrojejunal ulcer and gastric ulcer by ourselves, by Ruffin, Grimson and Smith from Duke University, by Moore and his associates from the Massachusetts General Hospital and by Colp from Mount Sinai Hospital, New York. Eighty-six per cent of Dragstedt's patients had duodenal ulcer and 9 per cent had gastrojejunal ulcer. In our series, 68 per cent (thirty-four patients) had duodenal ulcer and 14 per cent had gastrojejunal ulcer. If the sixty-eight cases in which operations on the vagus nerves were performed by other surgeons at the Mayo Clinic are added, the percentages are 65 for duodenal ulcer and 29 for gastrojejunal ulcer. It is interesting to note that the percentage of patients operated on for duodenal ulcer and gastrojejunal ulcer reported by the others referred to, except Dragstedt, practically parallel those of the Mayo Clinic series (table 3).

Resection of the vagus nerves without associated operation on the stomach was done in only seventeen of our fifty cases and in thirty-one of the sixty-eight cases of our colleagues at the clinic. In ten cases of our group the operation was performed for duodenal ulcer. The reason for the small number of cases of duodenal ulcer in which this operation alone was carried out was that in the other cases of duodenal ulcer the ulcer was so large and seemed to be of such an obstructive or potentially obstructive nature that some type of drainage operation of the stomach, such as gastro-enterostomy and, in a few cases, gastric resection, was thought advisable and in cases of gastrojejunal ulcer it was considered worth while in most cases to remove the gastrojejunal ulcer and disconnect the gastro-enteric anastomosis at the time of vagotomy. In two cases the gastrojejunal ulcer and the gastro-enteric anastomosis were not removed.

In 87 per cent of the cases of duodenal ulcer at the Mayo Clinic medical

treatment has been employed in recent years. In the complicated cases of duodenal ulcer in which operation has been performed partial gastrectomy with partial duodenectomy has been the operation of choice. Resection of the vagus nerves has been performed in some cases of this type, in cases of gastrojejunal ulcer and in a few cases of gastric ulcer.

If resection of the vagus nerves were employed in more cases of duodenal ulcer in which the lesion is now treated medically, results of this operation might be expected to be better than they have proved in our series.

Small has made an intensive review of the literature relating to the effects of vagotomy in animals and the clinical results of patients with peptic ulceration. Time does not permit more than the briefest reference to these historical data. However, neither those working on the problem experimentally nor those working on it clinically to the tune Dragstedt's

TABLE 3
COMPARATIVE STATISTICS OF REPORTED VAGOTOMIES

	Cases	Duodenal ulcer		Gastrojejunal ulcer		Gastric ulcer	
		Cases	Per cent	Cases	Per cent	Cases	Per cent
Dragstedt.	170	147	86	15	9	8	5
Mayo Clinic							
Our series	50	31	68	7	14	0	16
Total series	118	77	65	31	29	7	6
Griffison....	57	40	70	10	18	7	12
Moore .	74	57	77	10	22	1	1
Colp... .	33	20	61	12	30	1	3

contribution was made were able to demonstrate to Small's satisfaction that a decisive viewpoint could be reached regarding results of the procedure either in animals or in patients.

One of the interesting contributions, in our opinion, indicating that results of vagotomy might be transitory, was that of Hartzell and Vanzant who showed that from six months to two years after resection of the vagus nerves of the stomach of dogs gastric acidity and motility returned to normal. The recent clinical reports of Moore and associates indicate that the same is likely to recur in some human beings.

INDICATIONS FOR RESECTION OF THE VAGUS NERVES

The greatest field of usefulness for resection of the vagus nerves seems to be in the treatment of ulceration after partial gastrectomy. Recently Priestley has reported on a collected series of sixteen cases of ulceration

after partial gastrectomy for which vagotomy was performed at the Mayo Clinic. Results were good in twelve, fair in three and poor in one case. In the same study in twenty-one cases of gastrojejunal ulcer after gastro-enterostomy good results have followed resection of the vagus nerves in nineteen cases, fair results in two and poor results in none. Despite these figures we are inclined to look with skepticism at this time on the chance that healing of a gastrojejunal ulcer developing after gastro-enterostomy will result from resection of the vagus nerves alone. The reason for this skepticism is a case which we have mentioned previously. In this case a perforating gastrojejunal ulcer developed and required partial gastrectomy approximately ten months after anterior gastro-enterostomy, resection of the vagus nerves and subsequent jejunojejunostomy (table 1). The result of the insulin test was negative in this case.

Resection of the vagus nerves has so far seemed to have merit in cases in which dyspepsia caused by chronic duodenal ulcer does not respond to a medical regimen and the duodenal ulcer at operation is found to be small and not obstructive and other operations are not necessary on the stomach. In the ten cases of our series in which this type of lesion was present resection of the vagus nerves has relieved the pain of ulcer at the expense, however, of dilation of the stomach with troublesome symptoms of disturbances of motility in three. When resection of the vagus nerves was combined with other operations, such as gastro-enterostomy, as it was in twenty-four cases of duodenal ulcer in our series, no improvement in the results is evident over those which experience of many years in many cases has shown occur when gastro-enterostomy or some other operation is performed without vagotomy. Although relief of ulcer distress occurred in twenty-two of our twenty-four cases, recurring ulceration necessitated gastric resection in one and troublesome disturbances of motility were present for at least nine months in six cases.

Resection of the vagus nerves has no place in the treatment of chronic gastric ulcer if the ulcer can be removed in the course of partial gastrectomy. In nine of our fifty cases resection of the vagus nerves was done for gastric ulcer. Recurrence of ulcer took place in one case and disturbances of gastric motility persisted for seven months or longer in three.

Experience and time will be required to tell just what place resection of the vagus nerves has in the treatment of duodenal and gastrojejunal ulceration.

In 1916, resection of the stomach for gastric ulcer was performed in 101 cases with a mortality rate of 2.0 per cent. In the same year gastric resection for duodenal ulcer was done in 296 cases with a mortality rate of 2.0 per cent. In view of the low mortality rate and good results in these cases, resection of the stomach and not resection of the vagus nerves seems on the whole to be the operation of choice for both duodenal and gastric ulcers.

SUMMARY OF RESULTS IN OUR SERIES

Resection of Vagus Nerves Alone.—In our series of fifty cases to date vagotomy alone was done without other procedure in ten for duodenal ulcer, in two for gastrojejunal ulcer and in five for gastric ulcer. All of the patients obtained relief of the pain caused by ulcer. In three cases of duodenal ulcer and in one of gastric ulcer disturbances of motility occurred

after vagotomy. In one case of duodenal ulcer and one of gastric ulcer the results of one insulin test in each case after operation were positive and in neither case was gastric acidity reduced. Four of the patients with duodenal ulcer were reported at dismissal (approximately two and a half to three weeks after operation) as still having visible ulcers on roentgenologic examination. Two of these patients gave a positive reaction to the insulin test.

Resection of Vagus Nerves and Other Gastric Operations.—Vagotomy with a *simultaneous gastric operation* was performed in twenty-four cases of duodenal ulcer, in five of gastrojejunal ulcer and in four of gastric ulcer. In twenty-two of the twenty-four cases of duodenal ulcer, in four of the five cases of gastrojejunal ulcer and in two of the four cases of gastric ulcer, relief of distress from the ulcer was obtained. Ulceration recurred in one case of gastric ulcer and in one case of duodenal ulcer and subtotal gastrectomy was necessary six and ten months later. In another case the gastric ulcer failed to heal, and in one case a duodenal ulcer recurred after excision of a gastrojejunal ulcer. In all, gastric acidity was reduced and reactions to the insulin test after vagotomy were negative. In six cases of duodenal ulcer for which vagotomy and associated gastro-enterostomy was carried out, in two cases of gastrojejunal ulcer and in three cases of gastric ulcer, moderate to marked disturbances of motility developed. Of these, one of the patients with duodenal ulcer who reacted negatively to the insulin test and one patient with gastrojejunal ulcer who reacted positively to the insulin test had no reduction in gastric acidity after operation.

SIXTY YEARS OF VAGOTOMY; A REVIEW OF SOME 200 ARTICLES*

WALTER C. ALVAREZ

It appears that in many individual animals and men vagotomy does little harm and can promptly bring about the cure of an ulcer.

In a few individual animals and men vagotomy produces much discomfort and ill health and, in animals, it can even result in decline and death. Why there is this individual difference is not yet known.

Vagotomy does not always protect animals and men from the production of ulcers. In fact, in some individual animals and men it leads to the production of ulcers.

Since vagotomy must usually be done in addition to gastro-enterostomy or partial gastric resection, what is most needed today is an answer to the question: Will vagotomy prevent the formation of a jejunal ulcer? Already, reports are coming in of cases in which a bad jejunal ulcer developed after vagotomy (Warren, 1947; Walters, 1947).

It is interesting that the flurries of interest in hi-vagotomy in the years 1907 to 1914, 1920 to 1924 and 1930 to 1934 died down. As so often happens, the reasons for surgeons' having given up the operation were not published.

* Abstract of paper published in full in *Gastroenterology*. 10 413-441 (Mar.) 1918.

A STUDY OF CERTAIN PROBLEMS RESULTING FROM VAGOTOMY IN DOGS WITH SPECIAL REFERENCE TO EMESIS*

KAO HWANG, HIRAM E. ESSEX AND FRANK C. MANN

An experimental study has been made in the dog before and after double vagotomy at different levels from the diaphragm anteriorly to the larynx. Particular attention has been paid to the mechanism of emesis after vagotomy at high levels as well as the nervous control of the esophagus and the cardia.

The functional changes after the various operations were studied roentgenologically with the aid of barium meals and catheterization with a soft rubber tube. Balloon studies were also made in many experiments.

The general behavior of these animals after the various operations has been described in detail in the complete paper. The development of frequent regurgitation and emesis was a common consequence after vagotomy was done at, and especially higher than, the level of the hilus of the lung. Similar, although much less severe, phenomena occurred when nutrition was maintained only by parenteral feeding.

The most important change after vagotomy at a high level in the dog is a complete loss of the peristaltic activity of the lower part of the esophagus. The lower two thirds of the esophagus were involved when vagotomy was done at any level above the arch of the aorta.

The paralyzed esophagus was shown to retain food material or secretions which might be either partly pushed down to the stomach or partly regurgitated, apparently by the aid of the diffuse tonic contraction of the whole esophagus as a response to the rapid distention. Mere retention of the food in the paralyzed esophagus or distention of the esophagus was not shown to be the cause of the nausea and vomiting.

The nausea and vomiting in these animals apparently resulted from irritation of the pharynx by the large amount of the regurgitated material. The response to the pharyngeal irritation was found to be more sensitive in many dogs after than before vagotomy. Coincidentally in another series of experiments the response to appropriate doses of apomorphine was found to be greater after than before vagotomy, a result that suggests a hyperexcitable status of the vomiting center.

The possibility of irritation of the sectioned nerve stumps as the cause of vomiting was eliminated by similar findings in dogs after the exteriorized vagus nerve had been blocked with procaine hydrochloride.

Similar consequences occurred after vagotomy in dogs on which complete sympathetic ganglionectomy had been performed.

After complete sympathetic ganglionectomy two dogs did not show any significant change of the function of the esophagus and the cardia and in a third dog the tone of the cardia was only slightly reduced.

The peristalsis of the lower two thirds of the esophagus is dependent on the extrinsic vagal supply. But it is not likely that the nerve supply to the

* Abstract of paper published in full in the *American Journal of Physiology*, 143:429-449 (May 1) 1947.

upper third is derived from the branches arising from the vagus posterior to the larynx.

The vagus contains both inhibitory and motor fibers to the cardia. There is evidence that the inhibitory fibers branch off from the main vagus trunks above the level of the arch of the aorta and take an intrinsic course in the esophageal wall to reach the cardia.

When the cardia was freed from vagal control its tone was never found increased but was reduced to different degrees in the majority of cases. In one dog the tone of the cardia was found not changed after complete sympathetic ganglionectomy but was reduced by subsequent double cervical vagotomy.

GASTROSCOPY IN THE DIAGNOSIS OF GASTRIC VARICES*

HERMAN J. MOERSCH

Severe gastro-intestinal bleeding is always a harrowing experience to the afflicted patient and a source of considerable concern to the attending physician. It is generally appreciated that severe gastro-intestinal bleeding is a frequent accompaniment of esophageal varices. It is not, however, generally appreciated that such hemorrhages may occur secondary to gastric varices, and most textbooks dealing with gastro-intestinal disease give scant attention to this possibility. This may be due, in part, to the fact that great difficulty may be experienced in the recognition of esophageal and gastric varices on roentgenologic examination, and also to the fact that such varices may even be overlooked at necropsy unless special effort is directed toward their detection.

Although roentgenographic examination of the esophagus is of paramount importance in the diagnosis of esophageal varices, experience at the Mayo Clinic has demonstrated that there is approximately a 30 per cent chance that esophageal varices will escape detection by this method of diagnosis and will be recognized only by esophagoscopy examination. It is doubtful that varices which involve the gastric mucosa will be recognized on roentgenoscopic examination in any higher percentage than varices in the esophagus will be recognized. It is, therefore, important that additional diagnostic aids be utilized if their presence is to be detected.

In the event of gastro-intestinal bleeding from either esophageal or gastric varices, there is always the problem of whether the bleeding point is situated in the esophagus or in the stomach. This is of more than academic interest inasmuch as the detection of gastric varices may play an important role in determining the type of treatment that is to be utilized in any given case. Gastroscopy can be of great value in the diagnosis of gastric varices. This fact was clearly demonstrated recently in a study of six cases of severe gastro-intestinal bleeding secondary to esophageal and gastric varices. In four of the six cases, roentgenologic examination of the esophagus and stomach showed the presence of both esophageal and gastric varices. In

* From the Bulletin of the American Gastroscopic Club, April, 1917.

the other two cases the result of roentgenologic examination was negative. On gastroscopic examination, gastric varices were found in all six cases. The two patients whose roentgenograms of the esophagus and stomach had been reported negative died later as a result of gastro-intestinal bleeding and at necropsy varices in both the esophagus and the stomach were found. Of especial significance was the fact that the source of bleeding in each case was a gastric varix.

Esophageal varices have long been regarded as a contraindication to gastroscopy. Although it is probably wise to avoid the passage of a gastroscope in cases of esophageal varices, I believe that the procedure can be used, when indicated, without undue risk to the patient if it is carried out with care and gentleness. So far, I have experienced no difficulty in gastroscopic examination of patients who have esophageal varices, and no complications have followed the procedure.

Gastric varices, as viewed through the gastroscope, have an appearance similar to that of esophageal varices as seen through the esophagoscope. The vessels appear tortuous and distended and are bluish in color. They are best seen when the stomach is only partially distended with air. If too much air is used to inflate the stomach, the vessels tend to become flattened and are much more difficult to visualize. They are most commonly seen along the anterior wall of the stomach near the lesser curvature just below the esophageal hiatus. The varices seldom extend down beyond the middle third of the stomach, although in one case I found them to extend as far down as the antrum. Care must be exercised in distinguishing gastric varices from gastric rugae. Gastric varices have a tendency to bisect rugae at an angle of about 45 degrees.

The possibility that the bleeding is from gastric varices must always be considered in any case of unexplained gastro-intestinal bleeding. Gastroscopy can be of definite aid in establishing the correct diagnosis in cases of this type.

FIVE, TEN, FIFTEEN AND TWENTY YEAR CURES OF CARCINOMA OF THE STOMACH FOLLOWING PARTIAL GASTRECTOMY*

WALTMAN WALTERS AND JOSEPH BERKSON

Before beginning a discussion of the results of partial gastrectomy in the treatment of cancer of the stomach I should like to call your attention to a phase of the study of survival rates which is based on the theory that resistance to growth of the cancer cells varies with different individuals. For example, what, other than this tissue resistant factor, will account for a survival rate of 29 per cent and a nonsurvival rate of 71 per cent among patients of the same age and sex with lesions of comparable size and degree of malignancy on whom the same operative procedure was carried out? What else will account for the survival, for five years or longer, of a few

* Read at the meeting of the Fourth International Cancer Congress, St. Louis, Missouri, September 2 to 7, 1947.

patients with microscopically proved carcinoma who have been denied removal of the lesion because of its extent, or on whom palliative procedures, such as gastro-enterostomy, to relieve obstruction or local excision have been performed?

A survival of five years or longer in some cases of gastric lesions of a high degree of malignancy following partial gastrectomy is a great stimulus to every surgeon to remove all such lesions if this is technically possible, on the other hand a discouraging fact is that in some cases in which lesions are of low degree of malignancy and prospects for cure seem to be excellent, recurrence of the carcinoma will develop in spite of gastric resections of magnitude equal to those done in cases of lesions of the most malignant type. The lesson of this seems to be that the human resistance factors must be determined and measures taken to improve them.

In 1942, Drs. Gray, Priestley and we with the assistance of Dr. Everett B. Lewis, Fellow and First Assistant in Surgery, in the Mayo Foundation and the Mayo Clinic, undertook a study of 11,000 cases in which a diagnosis of malignant lesions of the stomach had been made at the Mayo Clinic. Of these 11,000 patients, 6,352 underwent operations of which 2,810 were gastric resections. The detailed review deals mainly with cases in which treatment was surgical. These cases include all in which malignant lesions of the stomach were present and in which operation was performed at the Mayo Clinic up to and including 1938, with the exception of a small number of cases in which the patients were operated on before institution of an adequate record system.

In the great majority (99 per cent) of cases the lesion was carcinoma; in only a small fraction (1 per cent) was lymphosarcoma or fibrosarcoma observed. In the operative group with carcinoma the decade of fifty through fifty-nine years contained a larger percentage of cases (35 per cent) than any other decade of life, the decade sixty through sixty-nine years also contained a relatively large fraction of cases (29 per cent), and below and above these ages the proportion of cases decreased progressively. The mean age of these patients was fifty-five years. The distribution by age is almost identical for the cases in which resection was performed and for those in which only exploratory laparotomy or palliative operation was carried out. As a corollary of this, the relative proportion of cases in which the lesion was removable by resection is about the same (44 per cent) at all ages. The resectability rate has increased to 58 per cent during the past five years. This is largely attributable to the increased number of extensive resections, total gastrectomies and transthoracic resections for lesions of the cardiac end of the stomach. The hospital mortality rate in these cases at the clinic, 1908 through 1940, averaged 16 per cent but in the last five years (1942 through 1946) it has averaged 8 per cent.

In the study of the 11,000 cases great pains were taken to make the follow-up regarding survival accurate, and as complete as possible. We were able to trace more than 99 per cent of the patients for more than five years and more than 98 per cent of the eligible patients for more than twenty years. We reviewed carefully the errors inherent in the calculation of the survival rates, as they were found frequently in medical literature, and employed actuarial principles in calculation as a check on calculations made by simpler but less precise methods (fig. 5).

At present the only hope of cure for carcinoma of the stomach resides in establishing the diagnosis at a time when surgical removal of the growth

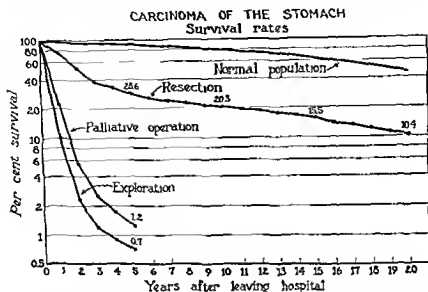


Fig. 5—Survival curves plotted on a logarithmic scale to illustrate the graphic interpretation of survival rates (From Walters, Waltman, Gray, H. K., and Priestley, J. T.: Carcinoma and other malignant lesions of the stomach. By permission of the publishers, W. B. Saunders Company, 1942.)

is possible. So far as is known, no patient ever has been cured of gastric carcinoma definitely by any means other than surgical intervention. Furthermore, from all present prospects the main opportunity to reduce

TABLE 1
CARCINOMA OF THE STOMACH—GENERAL DATA
Diagnoses established in 10,890 cases, 1907-1938

	Patients	Per cent of total (10,890)
No operation	4,648	42.7
Operation	6,242	57.3
Exploration only	2,431	22.3
Palliative procedure	1,039	9.5
Resection	2,772	25.5

the great number of deaths which this condition causes annually lies in establishing the diagnosis earlier in a greater proportion of cases so that more patients may be afforded the possible benefits of gastric resection.

This is not an easy feat, as at times the lesion, because of its location and inherent nature, may become actually inoperable before its presence is suspected.

Livingston and Pack emphasized that any consideration of ultimate results obtained in the treatment of gastric carcinoma should take into account first of all the entire number of cases in which the diagnosis has been established and subsequently determine how many of the patients have been cured.

The diagnosis of carcinoma of the stomach was made at the Mayo Clinic in 10,890 cases in the years 1907 through 1938 (table 1). Of these, the lesions in 1,618 (14.7 per cent) were considered to be inoperable and the patients received only palliative medical treatment. The remaining 6,242 (57.3 per cent) patients were subjected to exploratory operation with the hope that gastric resection might be accomplished. Of this group in which operation was performed, inoperable lesions were found in 2,431 cases (22.3 per cent of the entire series of 10,890 cases) and in each of these cases the incision was closed and nothing further was done. In another additional group of 1,039 cases (9.5 per cent of the original series of 10,890 cases) also inoperable growths were present but some form of palliative procedure appeared to be worth while and was performed. Thus, of the original series of 10,890 cases in which the diagnosis was established there were 2,772 cases or 25.5 per cent in which gastric resection actually was accomplished. This means that approximately one out of four persons for whom the diagnosis of gastric carcinoma was established at the clinic during these years had the lesions removed surgically and thereby, provided they survived the operation, these patients had some chance of ultimate cure. In our experience, then, the surgical rate of gastric carcinoma averaged 57.3 per cent over this period of years and the resectability rate (calculated on all patients) was 25.5 per cent. When the resectability rate is calculated on the basis of the group in which operation was performed, namely 6,242, it is found to be 44.4 per cent. This figure is important because, even though the surgical rate is high or gradually increases as time goes on it does not mean that the ultimate results actually are being enhanced unless by maintenance of a high resectability rate the actual percentage of cases in which resection is performed also is increased thereby.

Gastric resection was performed then in 2,772 cases (25.5 per cent) of the entire series in which the diagnosis of carcinoma was established. Obviously all of these patients for whom resection of the lesion was performed did not survive operation and those who died were thus just as definitely denied the possibility of cure as were those on whom operation was not performed. During this period of years the average mortality rate for all types of gastric resection, including total gastrectomy, was 16.2 per cent. This means that only 2,322 of the 2,772 patients who underwent resection actually survived the operation and therefore had a definite opportunity for ultimate cure. Thus, of the original group of 10,890 cases in which the diagnosis was established, in 2,322, or 21.3 per cent, were the patients afforded a chance of cure.

Of this group of patients who had resection performed and who survived the operation 28.9 per cent lived five years or longer, 20.4 per cent lived ten years or longer, 15.2 per cent lived fifteen years or longer, 10.5 per cent

lived twenty years or longer, and 6.3 per cent lived twenty-five years or longer (fig. 6).

Included in the calculation of these rates are all deaths regardless of cause. As will be pointed out later, five years subsequent to operation the mortality rates are close to normal, so that the decrement of patients after the five year mark is largely composed of normal deaths. If correction is made, for these deaths, the five year survival rate becomes 31.9 per cent. Since, as we have seen, only 21.3 per cent of the original group were subjected to resection of the lesions and survived operation, in terms of the original group of cases in which the diagnosis was established, 7 per cent of the patients survived five years or more.*

The average surgical rate in our experience has been 57.3 per cent, although in recent years it has risen to more than 60 per cent. In turn numerous factors determine the resectability rate, which of course is of

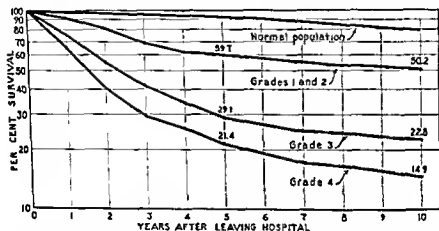


Fig 6—Effect of grade of malignancy on survival rates. Grade of malignancy is an important factor in prognosis. Graph shows survival curves in cases of carcinoma in which resection of stomach was carried out. Rates plotted on logarithmic scale so that slope gives death rate. After five years rates approach normal. (From Walters, Waltman, Gray, H. K., and Priestley, J. T. *Carcinoma and other malignant lesions of the stomach*. By permission of the publishers, W. B. Saunders Company, 1942.)

paramount importance. In general the resectability rate will increase with the surgeon's experience and skill. Obviously a lesion which a surgeon inexperienced in the field of gastric surgery might consider to be inoperable might be readily removed by a surgeon of greater experience in this field. This has to do with lesions in the upper part of the stomach and those perforating lesions necessitating removal of adjacent structures, such as transverse colon or mesocolon and portions of the pancreas.

The value for gastric acidity and the resectability rate appear definitely related (table 2). As the value for gastric acids increases, the resectability rate increases. Patients who have achlorhydria have a lower resectability rate in general than those who have some free acid present in the gastric contents. The full explanation of this relationship is not readily apparent;

* This estimation assumes that no patients for whom resection was not performed survived this length of time. Actually a small number did live for five years.

however, in general the more extensive lesion is apt to be associated with low acids or achlorhydria, whereas the smaller lesion is associated more frequently with higher values for free acid

TABLE 2
CARCINOMA OF THE STOMACH 1907-1934
Resectability rate according to gastric acidity

Free acids, units	Patients	Resections	
		Number	Per cent
Achlorhydria	2,093	1,222	40.8
1-9	219	107	48.9
10-19	554	275	49.6
20-29	523	285	54.5
30-39	366	203	55.5
40-49	236	149	63.1
50+	204	137	67.2

The effect of the gastric acids on the survival rate is interesting to note (table 3). In the group of cases in which free acid was present, the survival rate for five years in those in which the values for free acid were 30 units

TABLE 3
CARCINOMA OF THE STOMACH
Five year survivals according to gastric acidity

Free acid, units	Patients who survived operation		Lived five or more years after leaving hospital	
	Total	Traced	Number	Per cent of traced patients
Achlorhydria.	827	817	279	29.3
1 to 29	512	508	122	24.0
30 or more.	376	375	139	37.1

or more (Topfer's method) was definitely higher (37.1 per cent) than in those in which values for free acid ranged from 1 to 29 (24.0 per cent). In the group in which achlorhydria was present, interestingly enough, the survival rate was between the previous two figures, namely, 29.3 per cent.

Thus, those patients who had the ulcerous type of symptoms, which incidentally were often of relatively long duration, possessed a somewhat

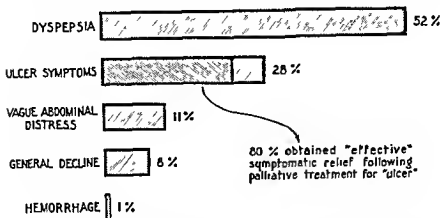


Fig 7.—First presumptive symptom caused by carcinoma of the stomach. In more than 50 per cent of the cases, indigestion was the first disturbance noted; in almost 30 per cent it was recurrent pain of ulcer-like character. The vagueness of the early symptoms is one of the reasons for late diagnosis. (From Walters, Waltman, Gray, H. K. and Priestley, J. T.: *Carcinoma and other malignant lesions of the stomach*. By permission of the publishers, W. B. Saunders Company, 1942.)

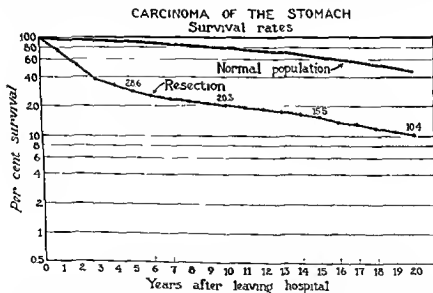


Fig 8.—Survival rates following resection of the stomach compared with the mortality rates among normal persons in comparable age groups. (From Walters, Waltman, Gray, H. K. and Priestley, J. T.: *Carcinoma and other malignant lesions of the stomach*. By permission of the publishers, W. B. Saunders Company, 1942.)

better chance of having resection performed if operation was carried out than those who presented the more usual symptoms of dyspepsia (fig. 7). Patients who had symptoms characterized more by debility and general

TABLE 4

CARCINOMA OF THE STOMACH 1907-1934 CASES IN WHICH RESECTION WAS PERFORMED

Hospital deaths postmortem findings

	Patients	Per cent
Peritonitis	155	42.2
Pneumonia	115	31.3
Myocardial failure	13	3.5
Nephritis	9	2.4
Pulmonary embolism	14	3.8
Empyema and other pulmonary complications	14	3.8
Hemorrhage	9	2.4
Obstruction, cachexia, and so forth	39	10.6
Total cases of necropsy	308	100
Necropsy not performed	82	
Total	390	

TABLE 5

CARCINOMA OF THE STOMACH CASES WITH RESECTION SURVIVAL RATES

Period after leaving hospital, years	Patients who survived operation*		Lived beyond indicated period	
	Total	Traced	Patients	Per cent of traced patients
5	1,968	1,951	564	28.9
10	1,595	1,577	317	20.4
15	1,053	1,013	157	15.5
20	650	620	65	10.5
25	503	502	19	3.8

* Inquiry as of January 1, 1940. The five year group comprises the patients operated on five or more years prior to time of inquiry, that is, in 1934 or earlier; the ten year group comprises those operated on in 1929 or earlier, and so forth. Hospital mortality is excluded in the calculation of survival rates.

decline or hemorrhage than anything else had the lowest resectability rate of all.

In this series of cases 16.2 per cent of the patients succumbed in the hospital after resection from causes listed in table 4. In recent years the hospital mortality rate has declined markedly and in the five year period, 1942 through 1946, it has averaged about 8 per cent.

Although survival rates as shown in table 5 and figure 8 do not reveal brilliantly satisfactory results perhaps as compared with the results of operation for certain other malignant conditions, such as carcinoma of the lip, cervix and uterus, situations in which lesions of low-grade malignancy are relatively more common, they are encouraging to the extent that they demonstrate conclusively that a certain number of patients who have carcinoma of the stomach can be cured by appropriate surgical measures.

TABLE 6
CARCINOMA OF THE STOMACH: CASES OF RESECTION
Five year survivals according to grade of malignancy

Grade	Patients who survived operation*		Lived 5 or more years after leaving hospital	
	Total	Traced	Number	Per cent of traced patients
1	29	29	25	86.2
2	190	167	110	59.8
3	316	315	95	30.2
4	270	266	62	23.3

* Inquiry as of January 1, 1946. Included here are patients operated on five or more years prior to time of inquiry, that is, 1934 or earlier. Hospital mortality is excluded in the calculation of survival rates.

Broders' method of classification of grade of malignancy supplies a most valuable prognostic omen (table 6). In a large group of cases it is observed that the lower the grade of malignancy of the lesions the better is the prognosis and, conversely, the higher the grade of malignancy the worse is the prognosis. After removal of lesions of grade 1 the five year survival rate is 86.2 per cent, whereas it decreases to 59.8 per cent after removal of lesions of grade 2, to 30.2 per cent in cases of grade 3, and to 23.3 per cent in cases of grade 4. Unfortunately, the majority of gastric carcinomas are of relatively high grade. Neither grade nor any other single factor, however, supplies adequate information in itself to serve as the entire basis for prognosis.

Next to the grade of the growth the presence or absence of involvement of the regional lymph nodes is of greatest significance (table 7). When resection was performed in the absence of involvement of regional lymph

nodes, the five year survival rate was 43.1 per cent as contrasted with only 16.5 per cent when regional lymph nodes were involved. The reasons for this striking difference in late results depending on involvement of lymph nodes are apparent. These data clearly emphasize the importance of removing all regions of lymphatic drainage from the stomach as completely as possible whenever gastric resection is performed. At times perhaps only one or two involved lymph nodes which are left behind may vitiate an otherwise successful result. If regional lymph nodes are not involved but growth has extended to certain neighboring structures, the survival rate for five years following removal of the growth and its extension is approx-

TABLE 7

CARCINOMA OF THE STOMACH

Five year survivals according to grade of malignancy and involvement of lymph nodes

	Patients who survived operation*		Lived 5 or more years after leaving hospital	
	Total	Traced	Number	Per cent of traced patients
Regional lymph nodes not involved	919	912	393	43.1
Grades 1 and 2	167	163	110	66.7
Grades 3 and 4	211	241	104	43.2
Ungraded . .	508	506	179	35.4
Regional lymph nodes involved	1,049	1,039	171	16.5
Grades 1 and 2 .	52	51	25	49.0
Grades 3 and 4	342	340	53	15.6
Ungraded	655	648	93	14.4

* Inquiry as of January 1, 1940. Included here are patients operated on five or more years prior to time of inquiry; that is, in 1934 or earlier. Hospital mortality is excluded in the calculation of survival rates

imately 5 per cent less than if such direct extension had not existed. By comparison direct extension of the lesion to nearby tissues influences the ultimate survival rate virtually not at all, provided regional lymph nodes also are involved at the time of resection. In other words, invasion of the adjacent lymphatic structures is of more significance as regards prognosis than is direct extension of the lesion, provided of course that this extension can be removed. It is interesting to note the effect of grade of malignancy and involvement of lymph nodes, when considered together, on the ultimate survival rate (table 7). As might be expected, lesions of grades 1 and 2 without involvement of lymph nodes are associated with the most favorable

prognosis, namely, a survival rate for five years of 66.7 per cent. Removal of lesions of grades 3 and 4 without nodal involvement is followed by a survival rate for five years which is comparable to that for extirpation of lesions of low grade which are associated with involvement of lymph nodes (43.2 per cent as compared with 49.0 per cent). The lesions of high grade of malignancy associated with involvement of lymph nodes offer the poorest prognosis (a five year survival rate of 15.6 per cent).

It is interesting to note the influence of the age of the patient on the survival rate (table 8). Although for some time many surgeons have had the thought that the young patient who has a malignant lesion removed does not have as good a chance for ultimate survival as the older patient

TABLE 8

CARCINOMA OF THE STOMACH 1907-1938: CASES WITH RESECTION
Five year survivals according to age

Age, years	Patients who survived operation*		Lived five or more years after leaving hospital		Survival rate adjusted for normal death rate
	Total	Traced	Number	Per cent of traced patients	
Less than 40	174	171	43	25.1	26.0
40-49	499	434	129	29.7	31.2
50-59	715	710	207	29.2	32.2
60-69	536	532	151	28.0	33.8
70+	101	101	31	29.8	49.3
Total	1,968	1,951	561	28.0	31.0

* Inquiry as of January 1, 1940. Included here are patients operated on five or more years prior to time of inquiry, that is, in 1934 or earlier. Hospital mortality is excluded in the calculation of survival rates.

who has been treated similarly, data pertaining to this opinion have been somewhat confusing. If such survivals are calculated according to age directly, the results obtained may be misleading. If, however, necessary corrections are made for the average death rates of the general population of similar ages it is seen that of those who survive gastric resection, younger patients have less likelihood of surviving five years after operation than do older persons. This difference ranges from a five year survival rate of 26.0 per cent following resection among patients less than forty years of age to a survival rate of 49.3 per cent among patients seventy years of age and older when the survival rate is adjusted for the normal death rate according to age. Reasons for this difference in survival at various ages of the patient are not definitely known but many interesting conjectures arise.

In concluding this brief report it is necessary to make some reference to two groups of cases which we are studying intensively, namely, the ten patients who survived five years after palliative operations, and the group of twelve patients whose lesions were thought to be malignant and inoperable but who also survived for five years.

We recently have reviewed the case records of these patients. In only one of the patients who had palliative operations and in three who had exploratory operations only, has the surgical diagnosis of carcinoma been verified by pathologic examination of a specimen from the lesion or from a gland adjacent to it. In the other cases, grossly the lesion appeared to be malignant and in most cases involved the posterior wall of the stomach with penetration to the pancreas, or the transverse mesocolon or both. The probability is that the lesions in which biopsy was not carried out were extensive inflammatory ones, as illustrated by the following case:

The patient, a man aged fifty-three years, presented himself at the Mayo Clinic on March 10, 1941, at which time a diagnosis of a large ulcerating lesion on the lesser curvature of the stomach was made. The gastroscopists stated that "although it appeared to be benign, inhibition around its edge and the fact that obstruction was encountered on introducing the gastroscope would seem to favor a neoplastic infiltration with secondary ulceration." They further commented that the entire picture grossly simulated that seen in lymphosarcoma. The roentgenologic report was that of a large gastric ulcer high in the posterior wall near the lesser curvature.

On April 2, 1941, an exploratory operation was performed and a perforating lesion of the stomach involving practically the entire upper third near the insertion of the esophagus was found. It was stated by the surgeon that it would have been impossible technically to remove the growth as it was attached posteriorly and there was no tissue available for biopsy without opening the stomach, which opening might not have lent itself to safe closure.

Following this procedure the patient continued to have ulcer type of pain with extension through to the back. Relief of pain was obtained from an ulcer regimen.

On May 28, 1947, subtotal gastrectomy was performed. A huge ulcerating gastric lesion located just below the esophagus on the posterior wall near the lesser curvature of the stomach which had perforated to the pancreas was removed. The crater was 3.5 cm. in diameter and the region of induration extended 2 cm. in each direction which necessitated removal of two thirds of the stomach. The pathologist reported the finding of a benign chronic gastric ulcer. The patient recovered from his operation.

Recently one of us (W. W.) operated on another patient with an even larger chronic perforating lesion which involved practically the entire lesser curvature of the stomach and extended into the pancreas, liver and anterior abdominal wall. This lesion was removed and was reported to be inflammatory yet both clinically and grossly it appeared malignant.

On another occasion a detailed report will be made of the four patients who had carcinoma of the stomach which was proved by microscopic examination of an involved node or a specimen from the lesion and who survived five years without extirpation of the lesion or without subsequent treatment either directed toward removal or destruction of the lesion or inhibition of its growth. If we calculate the survival rate including only those in which pathologic confirmation of the diagnosis was available, only 0.1 per cent of the patients who had palliative operations survived the five year period and only 0.2 per cent of those on whom exploration only was carried out. It must be remembered, however, that among the eighteen cases in which the surgical diagnosis of malignancy was not confirmed by pathologic examination and who survived the five year period, some malig-

nant lesions may have been present. In some cases in which there has been no pathologic confirmation of the surgical diagnosis of inoperable malignancy in the clinic and the patients have died at home, necropsy has confirmed the surgical diagnosis. We intend to make a further study of these cases in which the condition was surgically diagnosed as inoperable to learn whether or not postmortem examinations were made, and the type of lesion found.

The corollary, however, is obvious, namely, that survival rates should not include cases of carcinoma of the stomach unless the lesion can be proved malignant on microscopic examination of a specimen of the lesion itself or its adjacent lymph nodes.

SUMMARY

Of an original group of 10,890 cases in which a diagnosis of carcinoma of the stomach was made, gastric resection was performed in 2,772 (25.5 per cent) of the cases. The survival rates for patients with resection were as follows: five years or longer 28.9 per cent, ten years or longer 20.4 per cent, fifteen years or longer 15.2 per cent, twenty years or longer 10.5 per cent, twenty-five years or longer 6.3 per cent.

In the study of the 11,000 cases great pains were taken to make the follow-up regarding survival accurate, and as complete as possible. We were able to trace more than 99 per cent of the patients for more than five years and more than 98 per cent of the eligible patients for more than twenty years.

As the value for gastric acids increases, the resectability rate increases. In the group of cases in which free acid was present, the survival rate for five years in those in which the values for free acid were 30 units or more (Tüpfel's method) was definitely higher (37.1 per cent) than in those in which values for free acid ranged from 1 to 29 (21.0 per cent).

Brodsky's method of classification of grade of malignancy supplies a most valuable prognostic omen (table 6). In a large group of cases it is observed that the lower the grade of malignancy of the lesions the better is the prognosis and, conversely, the higher the grade of malignancy the worse is the prognosis.

When resection was performed in the absence of involvement of regional lymph nodes, the five year survival rate was 43.1 per cent as contrasted with only 16.5 per cent when regional lymph nodes were involved. Younger patients have less likelihood of surviving five years after operation than do older persons. This difference ranges from a five year survival rate of 26.0 per cent following resection among patients less than forty years of age to a survival rate of 49.3 per cent among patients seventy years of age and older when the survival rate is adjusted for the normal death rate according to age.

Of patients who had palliative operations only, 0.1 per cent with pathologically verified diagnosis of malignancy lived five years or longer and of those who had inoperable lesions reported at exploration and also pathologically verified 0.2 per cent lived five years or longer.

Although mortality rate for the entire series averaged 16 per cent for the years of 1907 through 1910, in the five year period, 1912 through 1916, this mortality rate has averaged approximately 8 per cent.

CARCINOMA OF THE STOMACH: ITS INCIDENCE AND DETECTION*

B R KIRKLIN AND JOHN R HODGSON

Carcinoma of the stomach, even after many years of investigation, remains one of the great unsolved problems of medicine. It is estimated that approximately 40,000 persons will die of carcinoma of the stomach in the United States this year; that roughly a third of all deaths attributed to carcinoma will be due to gastric carcinoma, and that deaths from carcinoma of the stomach occur in thirty of every 100,000 of population in the United States. From 1939 to 1944 inclusive, 103,142 roentgenologic examinations of the stomach were done at the Mayo Clinic. From this total the diagnosis of carcinoma of the stomach was made by the roentgenologist in 2,464 cases. This number includes those cases in which the roentgenologist suspected carcinoma as well as those in which he made a positive diagnosis. Approximately 2.4 per cent of the total number of patients having roentgenologic examinations of the stomach at the clinic have gastric carcinoma. The incidence of carcinoma of the stomach, diagnosed by roentgenologic means, in all patients coming to the clinic, was approximately 0.3 per cent.

Carcinoma of the stomach has continued to exact its price in lives in spite of the clinician's and roentgenologist's efforts toward earlier diagnosis and in spite of the surgeon's efforts toward cure. Obviously as long as the cause of carcinoma is unknown, we must continue to investigate thoroughly, without prejudice, all avenues of approach to the problem of getting the patient with carcinoma of the stomach into the hands of the surgeon as early as possible. At present the percentage of five year cures of carcinoma of the stomach is pitifully small compared to the incidence of the disease. Pack and Livingston reported that approximately 2 per cent of patients who have had carcinoma of the stomach are alive at the end of five years. Walters, Gray, and Priestley reported 7 per cent of the patients alive after five years. Unfortunately in a large percentage of cases, carcinoma of the stomach is inoperable before the patients reach the surgeon, and exclusive of palliation there is little he can do after metastasis has occurred. However, the surgeon has effected a cure in carcinoma of the stomach in a sufficient number of cases to prove that it is possible, and as long as surgery is one of our chief weapons, if not the only effective one, against this disease, it follows that careful consideration must be given to any suggestion which would enhance the earlier diagnosis of carcinoma of the stomach.

It has been suggested that survey studies be made in persons in older age groups for the purposes of detecting carcinoma in its beginning stages. It would be fortunate indeed if roentgenologic examination could be demanded for every patient who has symptoms and signs which even by remote chance might have their origin in organic disease of the stomach or duodenum. However, after careful consideration we have concluded that survey examinations of the stomach for the purposes of detection of carcinoma of the stomach are entirely impractical.

* Read at the meeting of the American Roentgen Ray Society, Atlantic City, New Jersey, September 18 to 19, 1947.

The objections to survey studies are many and varied. Saltzstein and Sandweiss reviewed the symptomatology in 257 cases of gastric carcinoma. In 24.7 per cent of the cases the malignant disease was preceded by long-continued indigestion. In 75.3 per cent of the cases clinical evidence of disease appeared suddenly in persons previously in good health. A similar experience was reported by Gray in which 75 per cent of his patients had symptoms less than one year and 40 per cent of the total had symptoms less than three months prior to diagnosis.

We reviewed 192 cases of carcinoma of the stomach and our results confirmed the findings previously published by Gray. Of the total of 192 patients we found that 75 per cent had had symptoms for one year or less.

Slightly less than a third of the total group had had symptoms for three months or less, which is a slightly smaller percentage than the 40 per cent mentioned by Gray. More than half of the total number had had symptoms less than six months before diagnosis. Although carcinoma of the stomach usually has begun its growth before the onset of symptoms there is a correlation between the appearance of the tumor and the onset of symptoms. Therefore, since such a high percentage of patients have symptoms less than three months, it is reasonable to assume that if surveys are to be made, they must be made at least every three months. Three months is not a very long time in the life of a patient but it is a long time for the patient if a malignant lesion is developing. In occasional cases in which we have examined the stomach without finding a lesion, two or three months later we have found that carcinoma has developed. Wangensteen, in a recent article on this subject, listed the names of Johannes von Mikulicz, W. J. Mayo, D. P. D. Wilkie, Martin Kirsner and R. D. Carman as well-known authorities on the subject of gastric carcinoma who failed to recognize the disease in themselves until it was too late. Surely, if we are going to attempt to find these lesions early the routine survey study on older persons must be done every three months. If examinations are done less often than every three months, the purpose for which the examination is being done will be defeated since 75 per cent of these people have symptoms for less than one year anyway and the large majority of those who have the disease will have sought medical attention in the interval between periodic examinations.

What would it take to examine people more than forty years of age for carcinoma of the stomach? Easterman and Balfour have stated that 95 per cent of all carcinomas of the stomach occurs in patients more than forty years old. Obviously persons more than forty years of age are the ones that should be examined. This group comprises about 30 per cent of our population or 42,000,000 people. It would take 1,917.6 roentgenologists examining a stomach every two minutes for eight hours steadily every day of the year, including Sundays and holidays, year after year continuously to make a satisfactory survey of this group of people every three months.

It has been suggested that earlier diagnosis, which would be the object of examining more people, would lead to more persons being cured. The argument is, of course, that the earlier that the lesion is found the better the surgical results may be. If this is true then those patients who have a relatively short history should be those with the best chance of survival. In sixty-one of the total of 192 cases reviewed, symptoms had been present

for three months or less. In thirty-one cases or slightly more than half of this group the lesions were inoperable at the time the diagnosis was made. In 53 per cent of those cases in which symptoms had been present for six months or less, the lesions were inoperable at the time of diagnosis. If the lesions in half of these cases are inoperable after less than three months of symptoms, how much good would it do to make examinations once a year? Interestingly enough the lesions of only 37.5 per cent of those patients who had noticed symptoms for a year or better were inoperable at the time of diagnosis. It would seem that in order to get these patients into the hands of the surgeon in time, all of the people more than forty years of age must be examined before symptoms begin. Obviously, as we have already pointed out, this is impossible and impractical.

It has been said that carcinoma of the stomach is a public health problem. If carcinoma of the stomach is a public health problem, then all forms of cancer are within the realm of public health. So is heart disease and so is hypertension and so is the entire problem of disease. Communicable diseases are rightfully a public health problem and survey studies for tuberculosis, a highly infectious disease, are useful and practical. If all of medicine is a public health problem then medicine itself should be controlled by the public health department and therefore by the state. We neither believe that carcinoma is a public health problem nor can we agree that the solution to the problem of carcinoma of the stomach is in the direction and control of our efforts by the state.

Carcinoma of the stomach is one of the most insidious forms of malignant disease. Results with some of the other forms of carcinoma are considerably less discouraging than with gastric malignancy. Although we are in accord with any effort to reduce the yearly loss of life from this disease, we believe that our efforts should be along lines that are practical and designed to yield the greatest return.

We further believe that one of the most important parts of the campaign against cancer is the continued education of the public to an awareness of cancer. We believe that this should be augmented and that this alone will bring many patients to the physician in time. In any event the public must be educated before any attempt to survey is tried. They should know why they have to be examined once every three months, or the reaction will be, "Well, I had my stomach examined three months ago. I'm all right. Why do it again?"

We firmly believe that all forms of research dealing with carcinoma must continue to enjoy our full support and encouragement. As is true of any disease, until its etiology is known, everyone is working in the dark.

The final answer to the difficult problem of carcinoma of the stomach is not in earlier diagnosis or in surgical intervention although they constitute our only hope now. Some bright morning we shall awake to learn that the answer has been found, and then the direction of all efforts will be clearly outlined, because we will be working in the clear sunlight of truth.

TOTAL GASTRECTOMY WITH ESOPHAGODUODENAL ANASTOMOSIS*

JAMES T. PRIESTLEY AND FRANK KUMPUKIS

Although Merrem performed the first total gastrectomy in an experimental animal in 1810, Schlatter in 1897 was the first to perform this operation successfully in man. Since that time it has been employed in a limited number of cases, mostly in the treatment of cancer. Because of three main reasons this operation has not been used extensively; namely, (1) the technical difficulty of its execution, (2) the high operative mortality and (3) the poor late results. At present, these factors have been overcome only partially and, therefore, the procedure is still used with relative infrequency. Excellent articles dealing with total gastrectomy have been contributed by Finney and Rienhoff, Pack and McNeer, Graham, Ransom, Waugh and Fahlund, Lahey and others, and the subject has also been reviewed by Walters, Gray and one of us.

It is not the purpose of this paper to review the subject of total gastrectomy in general, but only to draw attention to one method of restoration of gastro-intestinal continuity after complete removal of the stomach, which has received little consideration in recent years. Although esophagojejunostomy probably should remain the anastomosis of choice in the majority of cases, end-to-end suture of the esophagus to the duodenum can be used with certain advantages in selected cases. Esophagoduodenal anastomosis is not a new procedure because Brigham reported the first successful use of it in 1898.

According to Pack and McNeer (tabulation), esophagoduodenostomy was

TABULATION

RESTORATION OF GASTRO-INTESTINAL CONTINUITY AFTER TOTAL GASTRECTOMY. TYPES OF ANASTOMOSIS (PACK AND MCNEER)

Years	Esophagojejunostomy			Esophagoduodenostomy		
	Cases	Per cent of total	Mortality, per cent	Cases	Per cent of total	Mortality, per cent
1881-1900	71	44.0	42.4	31	41.5	11.9
1901-1920	37	61.9	47.0	17	29.8	41.2
1921-1932	134	95.1	33.8	6	3.7	33.3

employed in 11.5 per cent of the seventy-five cases in which total gastrectomy was performed between the years 1881 and 1920. The mortality rate in these cases was 41.9 per cent, as compared with a mortality rate of 12.4 per cent in the cases in which an esophagojejunal anastomosis was estab-

* From the Archives of Surgery 22: 113-134 (Feb.) 1934.

lished. In contrast, during the years 1921 to 1930 esophagoduodenostomy was performed in only 20.8 per cent of fifty-four cases in which total gastrectomy was performed, and the mortality rate was 41.2 per cent in comparison with a rate of 27.0 per cent for the cases in which the esophagus was joined to the jejunum during the same period of years. As an obvious result, during the years 1931 to 1942 an esophagoduodenal union was established in only 3.7 per cent of the 160 cases in which the stomach was completely removed, but in this small group the mortality rate (33.3 per cent) was almost identical with that (33.8 per cent) in the cases in which the esophagus and jejunum were united. It is apparent at once that for one reason or another esophagoduodenostomy has been employed very infrequently during the last fifteen years, and that many surgeons who today have an extensive surgical practice have never employed this type of anastomosis.

Our interest in this subject was stimulated by two recent cases in which the pathologic process and anatomic relationships were such that the duodenum could be readily anastomosed to the esophagus after removal of the entire stomach.

REPORT OF CASES

Case 1.—A white man sixty-five years old was admitted to the hospital on February 28, 1916, with a thirty-five year history suggestive of duodenal ulcer, characterized by periodic epigastric distress and repeated gastro-intestinal hemorrhages. A recent hemorrhage was the cause of the patient's admission to the hospital at the time we saw him. Examination revealed that the hemorrhage was not severe and that the patient's general condition was good. The patient weighed approximately 125 pounds (56.7 kg.). Roentgenographic examination of the stomach was reported to show an old duodenal ulcer. Gastric acidity was not studied because of the recent bleeding.

After a few days of study and preparation, operation was performed on March 6, 1916. Surgical exploration revealed no demonstrable duodenal ulcer; however, high on the lesser curvature of the stomach, immediately adjacent to the esophagus, was an ulcerating lesion of indeterminate nature. Because of the definite possibility of a malignant process, the lesion was removed, and this required total gastrectomy. The duodenum was mobile, so an end-to-end esophagoduodenal anastomosis was established. The pathologist reported that the specimen consisted of the entire stomach and 5 mm. of the duodenum and 5 mm. of the esophagus. There was a chronic, hemorrhagic, perforating, inflammatory ulcer with a crater 2 cm. in diameter, situated at the esophagogastric junction.

The postoperative course of the patient, to the time of this writing, has been satisfactory. He was dismissed from the hospital on the fourteenth postoperative day. He returned to work several weeks later and has been working daily since that time. He weighed 20 pounds (9.1 kg.) less than his normal figure when he was discharged from the hospital. When he was examined eight months postoperatively he had gained 10 pounds (4.5 kg.) and the value for hemoglobin was normal.

Case 2.—A woman sixty-six years old registered on March 27, 1916, because of loss of weight (38 pounds or 17.2 kg.) during the previous two months and the more recent development of nausea and vomiting. Examination revealed a rather weak woman who weighed only 110 pounds (49.9 kg.). Roentgenographic investigation revealed an obstructing lesion in the region of the pylorus. The stomach still contained barium which had been administered five days previously.

After adequate preoperative preparation, operation was performed on April 3, 1916, at which time total gastrectomy, with removal of the omentum, and end-to-end esophagoduodenostomy were performed. A linitis plastica type of carcinoma was seen to involve virtually the entire stomach. The pathologist reported that the lesion was a grade 4 scirrhous adenocarcinoma with multiple portions of mucosal ulceration and involvement of the submucosa of the attached portions of the duodenum and esophagus. There was also invasion of the malignant process in the serosa of the stomach, regional lymph nodes and omentum.

The early postoperative course was complicated by atelectasis; the patient did not leave the

hospital until the twenty-third postoperative day. She was readmitted four days later because of empyema which required open drainage. Her condition improved gradually, and she was dismissed eighteen days later. There was no indication that the type of esophageal anastomosis established was in any way associated with the pulmonary complications. The patient succumbed six months later, from the malignant process.

SELECTION OF PATIENTS

Obviously, it is not feasible to bring the ends of the esophagus and duodenum together without tension and with an adequate blood supply to both parts in every case in which total gastrectomy is performed. In fact, no attempt should be made to establish such a union in all cases. However, in the thin, asthenic type of person, whose costal margins form an acute angle at the xiphoid process, and whose viscera frequently are more mobile than those found in the average patient, the duodenum can be joined to the end of the esophagus, easily and with no tension. It is in this type of patient that establishment of such an anastomosis is suggested and recommended. In one of the cases reported it was unnecessary to mobilize the duodenum in any way. In the other case the lateral peritoneal attachment of the duodenum was incised for a distance of a few centimeters. This can be done without interference to the blood supply of the duodenum. We do not know the exact percentage of cases in which such an anastomosis is practical, but if it is kept in mind as a possibility we believe that it will be found applicable in a fair percentage of cases. Perhaps our interest in this subject has been stimulated by our more widespread use of the Billroth I type of anastomosis, with the Schoemaker modification, during the last several years, in the treatment of both duodenal and gastric ulcers as well as in selected cases of small malignant lesions in the region of the pylorus. Usually, the thick-chested, heavy set person who commonly also has a short neck, is not a suitable candidate for either esophagoduodenostomy or a Billroth I type of operation. Decision as to the establishment of esophagoduodenal anastomosis, in general, must be deferred until the abdomen has been opened and the situation thoroughly surveyed.

TECHNIC

The technical execution of total gastrectomy with esophagoduodenal anastomosis is not difficult when it is performed for a properly selected patient. In brief, after the abdomen has been opened and it has been decided that total gastrectomy is advisable, the surgeon proceeds with mobilization of the stomach in the usual manner (fig. 9). The duodenum is severed immediately distal to the pylorus, if there is no pathologic process present in this area. The duodenal stump is held in a curved forceps or similar type of clamp and is not closed unless it is apparent or becomes apparent that union of the esophagus and duodenum cannot be accomplished without tension. The surgeon then continues to free the stomach until it is attached only to the esophagus. The stomach should be emptied by suction or a clamp should be placed across the proximal portion of the cardia before the stomach is reflected upward and outward at the cephalad end of the incision, in order to prevent regurgitation of gastric contents into the esophagus. Then the end of the duodenum is approximated to the esophagus to determine whether it will lie in this position freely and without the exertion of traction on its attachments.

If such is not the case, the peritoneum lateral to the duodenum may be incised for a few centimeters, and gentle mobilization of the duodenum with no interference to its blood supply may be accomplished. If the duodenal

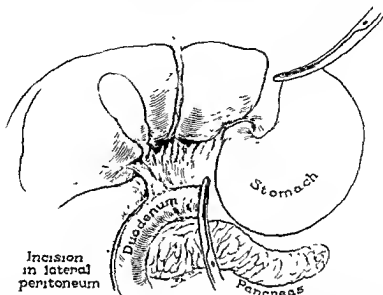


Fig 9—First step in performance of total gastrectomy and establishment of esophagoduodenal anastomosis. The stomach is mobilized completely except for its attachment to the esophagus. The duodenal stump is held in an appropriate type of clamp. If necessary, the duodenum is mobilized by an incision in its lateral peritoneal attachment.

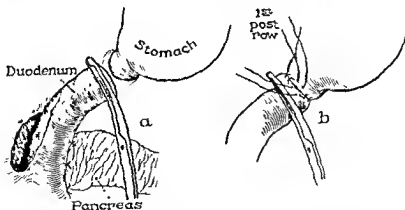


Fig 10—Esophagoduodenostomy (continued) (a) after it has been determined that the duodenum can be approximated to the esophagus without tension, the duodenum is anchored to the pancreas with approximately three interrupted sutures; (b) the first posterior row of interrupted sutures of silk is placed between the duodenum and esophagus.

stump still does not lie freely in approximation with the esophagus, this type of anastomosis should be abandoned, the duodenal stump should be closed and esophagojejunostomy should be performed.

If it is found that the duodenum will lie in contact with the esophagus

when all traction is removed, the surgeon may proceed with anastomosis of these two structures. First, two or three, preferably three, interrupted stitches of silk are placed between the posterior aspect of the duodenum and the pancreas (fig. 10a). These stitches, which constitute no part of the

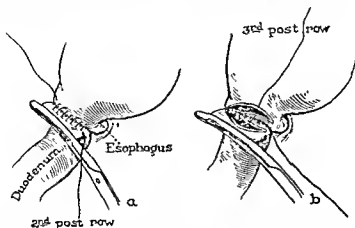


Fig 11.—Esophagoduodenostomy (continued): (a) a second posterior row of continuous silk suture is completed, (b) the third and innermost posterior row of suture of chromic catgut is placed in the mucosa of the duodenum and esophagus

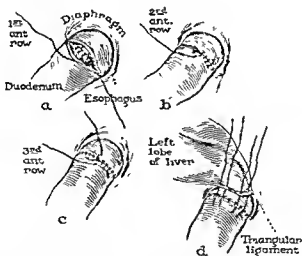


Fig 12 —Esophagoduodenostomy (continued): (a, b and c) three rows of sutures are placed anteriorly to correspond with those placed posteriorly; (d) the edge of the left triangular hepatic ligament is sutured to the duodenum, several centimeters below the completed anastomosis

anastomosis and are placed at least 3 or 4 cm. from the junction of the esophagus and duodenum, serve to fix the duodenum in its approximation to the esophagus. We prefer a three-row suture technic which consists of the placing of an outer row of interrupted stitches of silk (fig. 10b), followed by a continuous row of silk (fig. 11a) and, finally, a row of catgut in the

mucosa (fig. 11b). The posterior rows are placed first, from without in, so that the mucosal row is the last of the posterior suture lines to be completed. The esophagus is left intact until the posterior mucosal row is started, and then an incision is made transversely across the posterior wall of the esophagus (fig. 11b). At this time the esophagus is emptied by suction, if it has any contents. Next, the clamp is removed from the duodenum and the crushed tissue is trimmed away. After the posterior mucosal row of sutures has been completed, the anterior wall of the esophagus is incised gradually as the first anterior mucosal suture line is completed (fig. 12a). The outer two rows of sutures then are placed anteriorly (fig. 12b and c). After completion of the anastomosis, the duodenum is anchored in its new position anteriorly, just as it was anchored to the pancreas posteriorly. This may be done in one of two ways, depending on the convenience afforded by the local anatomic relationships. Usually, the left triangular ligament which attaches the edge of the left lobe of the liver to the diaphragm has been severed to aid immobilization and visualization of the esophagus. The severed edge of this ligament can be brought down over the anastomosis and sutured to the duodenum several centimeters below the anastomosis (fig. 12d). If this ligament is not approximated readily to the duodenum, the latter can be fixed with a few sutures to the undersurface of the left lobe of the liver.

COMMENT

It appears that anastomosis of the esophagus to the duodenum has been a rather forgotten procedure during the past fifteen years or so, and this without adequate justification. If the data collected by Pack and McNeer are referred to, and the mortality rates after both esophagoduodenostomy and esophagojejunostomy are examined, it is seen that for all years except 1921 to 1930 the rates are comparable. During this one ten year period the mortality rates favor esophagojejunal anastomosis, however, only seventeen cases of esophagoduodenal anastomosis were reported during this time, a number far too small to be statistically significant. Thus, the argument that a higher mortality rate is associated with this procedure hardly seems valid. When esophagoduodenal anastomosis is used indiscriminately, it is understandable that the risk might be greater, but if it is employed only in selected cases in which a well-established anastomosis can be accomplished without tension, there is little if any apparent reason why the risk should not be as low as that associated with any other procedure. In fact, there are some reasons to suspect that the mortality rate might be lower. In the first place, when it is performed under proper circumstances, the operation is easier of execution than esophagojejunostomy because there is only one loop of intestine to deal with, and this can be readily approximated to the esophagus. Moreover, there are fewer suture lines, because the stump of the duodenum is not closed. The questions of performance of entero-anastomosis and anterior or posterior colic types of anastomosis do not even arise for consideration.

In all types of surgery one principle which seems uniformly significant, even though the reasons for its importance may not always be apparent, is that the closer to normal the surgeon can leave the anatomic arrangement of the patient, other things being equal, the more nearly physiologically

ideal and desirable it seems. Thus, if the stomach is to be removed completely, the normal is approximated more closely if food enters the duodenum, rather than the jejunum, as it leaves the esophagus. In this manner it comes into direct contact with the digestive juices of the duodenum and follows a normal pathway from there on. It is obvious that our experience with this procedure has been too limited to permit dogmatic statements and conclusions to be formed. It has seemed warranted, however, that mention be made of certain technical advantages, as well as a few perhaps theoretic advantages, which this procedure possesses.

SUMMARY

Previous experience with esophagoduodenal anastomosis after total gastrectomy has been mentioned briefly. Two cases in which this type of procedure recently was performed have been presented. It was stressed that this procedure is suitable only in a selected group of patients. Technique for the operation has been briefly described. Esophagoduodenostomy is considered advantageous when practical because of its comparative simplicity and elimination of unnecessary suture lines, and also because of the more nearly normal anatomic and physiologic restoration of gastrointestinal continuity which results.

THE DISAPPEARANCE OF UROPEPSIN FOLLOWING TOTAL GASTRECTOMY IN THE RAT*

DONALD C. BALFOUR, JR., FREDERICK W. PRESTON AND JESSE L. BOLLMAN

A comprehensive review of the pepsin-like enzyme (uropepsin) present in the urine of animals has been recently compiled by Bucher. Although the fact that urine possesses proteolytic properties has been known since about 1860, accurate knowledge in regard to uropepsin was not possible until the introduction of the hemoglobin method of assay for pepsin by Anson and Mirsky and the adoption of this method for the assay of the enzyme in the urine by Farnsworth and associates and by Bucher. Many gaps in our knowledge of uropepsin exist; however, the following characteristics of the enzymes seem well established: (1) it is produced only in the stomach; (2) it enters the circulation at the level of the stomach, probably in the form of pepsinogen; (3) on activation by acid, uropepsin has a proteolytic action similar to that of pepsin; (4) the twenty-four hour output in the urine parallels the output of pepsin in the stomach, is relatively constant on a uniform daily menu and is increased when the protein in the diet is increased; (5) uropepsin is present in the urines of normal animals, is greatly diminished in patients with achylia gastrica and is absent after total gastrectomy.

This study is concerned with the rate of decrease of uropepsin in the urine following total gastrectomy.

* Abstract of paper published in full in *Gastroenterology*, 10: 890-892 (May) 1918

METHODS

Experiments were performed using the urine from gastrectomized rats. Complete removal of the stomach was accomplished. A direct end-to-end anastomosis between the esophagus and the duodenum was made. Sterile technique is not essential, and food and water may be given within the first twenty-four hours after operation. The animals were fed a standard laboratory purified food containing 21 per cent by weight of protein in the form of casein, 61 per cent carbohydrate, 8 per cent fat, and 1 per cent salt mixture containing adequate mineral and vitamin supplements.

Assays of the urine for uropepsin were done using a slight modification of the methods described by Farnsworth and associates and by Bucher. Urine was collected in metabolic cages where feces were withheld by a screen, and precautions were taken against contamination of samples with food and water. The urine was collected in beakers under xylene or toluene to prevent bacterial growth. Specimens that were contaminated with blood, saliva, mucus or liquid feces were discarded.

RESULTS

Excretion of uropepsin seemed to vary with the volume of urine excreted being greater when the volumes were large but more concentrated when the volumes were small. The daily urinary volume after gastrectomy was in the same range as before gastrectomy.

After total gastrectomy there was a rapid decline in the amount of uropepsin excreted in the urine. After the second day the amount of uropepsin detected was not significantly different from the amount obtained on the blank test made with the same sample after inactivation of the uropepsin with heat. The method is not sufficiently accurate to exclude the possibility of traces of uropepsin remaining after total gastrectomy. However, the data seem sufficiently clear to indicate that most of the uropepsin disappears within twenty-four hours after operation.

Immediately after gastrectomy the animals were given food but did not eat an appreciable quantity for five to ten days. To exclude the possibility that the decrease of uropepsin was due to fasting, two fasting rats were studied. No significant decrease of output of uropepsin was observed in these animals. No uropepsin has been found four months postoperatively.

INDICATIONS FOR AND ADVANTAGES OF SCHOEMAKER-BILLROTH I GASTRIC RESECTION*

O THERON CLAGETT AND JOHN M. WAUGH

The Billroth I operation, as it has been called since its original description, has had varying degrees of favor. A few years ago we recognized the advantages of this procedure and decided to use it in cases of gastric lesions in which it appeared feasible. The modification of the original Billroth I operation that we have used is essentially that of Schoemaker. It should

* Abstract of paper read at the meeting of the Western Surgical Association, Colorado Springs, Colorado, December 4 to 6, 1947.

be pointed out, however, that it is not very different from the modifications described by Billroth and by W. J. Mayo except that it accomplishes a more extensive resection, particularly along the lesser curvature. During the last five years we have performed this operation in 183 cases.

We recently have reviewed the records of these 183 patients. One hundred and forty-two of the patients were men and forty-one were women. Their ages ranged from twenty-seven to eighty-nine years. Two thirds of the patients were more than fifty years of age. As would be expected, most of these operations were performed for lesions of the stomach which did not involve the duodenum. Gastric resection with gastroduodenal anastomosis requires a mobile and relatively normal duodenum. Only occasionally can this operation be used in cases of duodenal ulcer. In such cases, fixation, shortening and narrowing of the duodenum usually will not permit a safe and satisfactory restoration of gastroduodenal continuity after gastric resection. A Billroth I resection can often be used to good advantage in cases of gastrojejunal ulcer because in many of these cases the original duodenal ulcer has healed and the duodenum is practically normal again. If the condition of the duodenum will permit it, we believe that a Billroth I resection is the surgical treatment of choice for duodenal and gastrojejunal ulcers. A Billroth I resection of three fifths or three fourths of the stomach and the pyloric ring will reduce the gastric acidity as effectively as any other type of resection of equal extent and will have additional advantages over gastrojejunal anastomosis. First, it can be performed more quickly and more easily; second, closure of the duodenal stump, the most vulnerable point in any gastric resection, is avoided, third, the duodenum has greater resistance to ulcer formation than the jejunum, and fourth, a more normal gastro-intestinal function will result.

The extent of the resection in this series has been measured in two ways: (1) by the surgeon's estimate of the portion of the stomach that was excised, and (2) by the pathologist's measurements made midway between the greater and lesser curvature. According to the surgeon's estimate, three fifths or more of the stomach was resected in 127 or 69.4 per cent of cases. By the pathologist's measurements fifteen or more centimeters of stomach was resected in ninety-seven or 53 per cent of the cases. We are convinced that an adequate gastric resection can be performed.

In four cases, a slight amount of leakage occurred for a few days but healing then occurred without incident. In two additional cases, separation of the anastomosis occurred and peritonitis developed and caused death. In one of these cases about seven eighths of the stomach was excised because of the presence of carcinoma. The patient had complete obstruction of the outlet of the stomach, had lost 60 pounds (27.2 kg.) and was a very poor candidate for any operation. In the other case, leakage occurred after resection for duodenal ulcer.

In our series of cases, gastric aspiration was not used routinely after operation. In nineteen cases (10 per cent), gastric retention which was associated with vomiting or required gastric aspiration occurred for from one to twelve days. This retention disappeared without difficulty or complication. In six additional cases, gastric retention necessitated a second operation. There were no deaths from this complication.

There were five deaths in the series, a mortality rate of 2.7 per cent. Three of these deaths occurred in cases of carcinoma, one in a case of duodenal ulcer, and one in a case of gastric ulcer.

From a technical standpoint, we would like to emphasize the importance of limiting this operation to those cases in which there is a suitable duodenum. As W. J. Mayo said, this procedure should not be forced. Tension on the anastomosis, even after extensive resection, can be avoided by mobilizing the stomach far up along both the lesser and greater curvatures and by mobilizing the duodenum by freeing it from its lateral peritoneal attachment.

Some of the advantages that we believe are offered by the modified Billroth I type of gastric resection are as follows: 1. It is the quickest and easiest type of partial gastric resection that can be performed. 2. It avoids the additional steps of duodenal closure and disturbance of the colon and mesocolon necessary in the more commonly performed gastric resections. 3. It accomplishes the objectives of gastric resection with a minimum of surgical trauma and handling of tissue. 4. It is a safe operation when used according to the indications mentioned previously. 5. It is a physiologic operation because it restores normal gastroduodenal continuity.

The chief contraindications to the use of the Billroth I resection for lesions that require gastric resection involve the duodenum. Fixation, shortening, narrowing or induration of the duodenum will prevent the establishment of a safe and satisfactory anastomosis. Under most other circumstances, the Schoemaker modification of the Billroth I operation provides a means of gastric resection that offers many advantages over the more commonly performed types of gastric resection.

REPORT OF PROLONGED FOLLOW-UP STUDY OF TWO PATIENTS WHO UNDERWENT PARTIAL GASTRECTOMY WHEN YOUNG*

PAUL E. MCGUFF AND CARL G. MORLOCK

The need for a major surgical procedure of any type on the stomach of a child is infrequent. Rarely, indeed, is it found needful to sacrifice the greater portion of a child's stomach. Because of this and the attention that has been drawn to the nutritional disturbances which sometimes follow partial gastrectomy, it seemed worth while to us to report two cases of patients who underwent partial gastrectomy when young and were followed up for a total of twenty-one and thirty years, respectively.

REPORT OF CASES

Case 1.—A child of ten years first registered at the Mayo Clinic because of gastro-intestinal bleeding. Three years prior to her admission, she had minor hematemesis and melena. Two months later a similar episode occurred. These episodes of bleeding continued to occur at intervals of three or four months and chronic moderate anemia resulted. Shortly before her admission epigastric pain developed, and a palpable epigastric mass was discovered.

* From *Gastroenterology*, 9: 307-312 (Sept.) 1947.



Fig. 13—Leiomyoma of stomach, 3 by 4 by 3 cm.



Fig. 14—Leiomyoma of stomach. Note extension of tumor to mucosal border and edema of tissue (hematoxylin and eosin, X50).

On examination, she was pale, measured 50 inches (127 cm.) in height and weighed 49 pounds (22.2 kg.). Epigastric tenderness and a palpable epigastric tumor were noted. The concentration of hemoglobin was 44 per cent (Hare, standard 13.77 gm. hemoglobin per 100

c. c. of whole blood), leukocytes numbered 5,100 and platelets, 251,000 per cubic millimeter of blood. Results of the Wassermann test were negative. A gastric analysis showed a total acidity of 38 clinical units and a free hydrochloric acid of 20 clinical units (Töpfer's method). Roentgenoscopic examination of the stomach demonstrated irregularity of the lesser curvature due to a tumor involving the wall of the stomach.

The patient was hospitalized and after she received a transfusion of 300 c. c. of citrated blood, abdominal exploratory operation was carried out. A tumor mass involving the lesser curvature of the stomach was encountered. The tumor, together with approximately two thirds of the lower portion of the stomach, was removed, gastro-intestinal continuity being restored by means of a posterior Polya anastomosis. The tumor measured 3 by 4 by 5 cm. and histologically proved to be a leiomyoma (figs. 13 and 14). An uneventful recovery followed.



Fig. 13 — Patient in case 1, twenty-one years after partial gastrectomy.

the operation. Contact with the patient was maintained by correspondence during the years following, but examination at the clinic was not made until the time of her second admission twenty-one years later.

She returned to the clinic at the age of thirty-one years because of rectal bleeding. She appeared to be in excellent general health and was engaged in a full-time teaching position. She had had no nutritional difficulty after her operation. She had developed normally, reaching her full height of 62 inches (about 158 cm.) at the age of eighteen years. She had always been slender, weighing no more than 110 pounds (50 kg.) at any time. Her eating habits were practically normal; she followed a routine of three regular meals and three lunches daily. Rarely did she experience epigastric distress except for mild postprandial discomfort after a large meal. She had no difficulty maintaining her weight. She tended to fatigue easily on moderate exertion and was rather susceptible to respiratory infections. Her menstrual periods began when she was fifteen years old and had been normal. For two or three years after the partial gas-

trectomy she had been given liver extract and iron because of mild anemia, but thereafter no treatment was needed to maintain a normal blood count.

On examination she was well developed (fig. 15) and weighed 105 pounds (47.6 kg.). Urinalysis revealed no abnormalities. Concentration of hemoglobin was 14.8 gm. per 100 cc. of whole blood, erythrocytes numbered 4,140,000 and leukocytes 8,000 per cubic millimeter of blood. Morphologic aspects of the blood cells were normal. Result of the Kline flocculation test for syphilis was negative. The fasting blood sugar was 74 mg. per 100 c.c. The total serum protein was 7.4 gm. per 100 c.c., the albumin-globulin ratio was 2.2:1. The basal metabolic rate was minus 4 per cent. Gastric analysis, after stimulation with histamine, revealed a total acidity of 20 chnical units and free hydrochloric acid of 10 chnical units. A dried twenty-four hour stool specimen, collected while the patient was on an average diet, showed a total fat ex-



Fig. 16—Roentgenogram made twenty-one years after lower half of the stomach was removed and a free Polya type gastroyejunal anastomosis was established.

cretion of 31.1 per cent which is within the normal range for the method employed. Proctoscopic examination gave negative results except for the finding of small internal and external hemorrhoids. Roentgenograms revealed that the thorax, colon and terminal ileum were normal. A roentgenogram of the stomach showed a freely functioning posterior Polya anastomosis (fig. 16).

Comment.—It is not often that one has an opportunity to follow up for a twenty year period a patient who underwent extensive partial gastrectomy in childhood. Berkman and Heck in 1945 called attention to three problems that may follow partial gastrectomy, any one of which may be of major concern to the patient. The first of these is a group of distressing postcibal symptoms sometimes grouped under the heading of "the dumping syndrome." The second is an inability of the patient to maintain weight and the third is persistent, often refractory, hypochromic microcytic anemia.

The patient stated that she had had no discomfort after eating except a mild sense of facial warmth after an unusually large meal. Significant nutritional difficulties had not been experienced at any time and there was no known abnormality of the concentration of hemoglobin or blood count for a period of twenty-one years after the operation.

After encountering the case just cited we searched the files of the clinic and found record of another patient who underwent partial gastrectomy and was followed up for a long period.

Case 2.—A white girl, sixteen years old, registered at the Mayo Clinic in 1917 because of vomiting and epigastric pain of one year's duration. She was found to be extremely underweight and profoundly anemic. A small, tender mass was palpable in the right upper quadrant of the abdomen. Urine was normal except for a few granular casts. Concentration of hemoglobin was 40 per cent. Erythrocytes numbered 2,900,000 per cubic millimeter of blood, leucocytes numbered 9,600. Gastric analysis showed a total acidity of 36 clinical units and free hydrochloric acid of 22 clinical units. A roentgenogram of the thorax revealed no abnormality. A roentgenogram of the stomach showed a prepyloric filling defect.

After preliminary transfusion of 500 c.c. of whole blood, partial gastrectomy was carried out for removal of the tumor and the lower fourth of the stomach. The tumor measured 3 by 2.5 by 2.5 cm. and proved to be a cellular fibroma. Gastro-intestinal continuity was re-established by means of an anterior Polya anastomosis. The recovery from the operation was without incident.

The patient has been followed up by correspondence for thirty years. Her digestion has been excellent always and she has been in good health except for some constitutional inadequacy and thinness. She has lived a normal life, has married and has had one child.

SUMMARY

Two patients who underwent partial gastrectomy early in life have been followed up for intervals of twenty-one and thirty years. Normal physical development and excellent health have been the experience of one. Half of this patient's stomach had been removed when she was ten years old. In the second case approximately a fourth of the stomach was removed. The patient was sixteen years of age. Postoperatively she developed normally and remained well for thirty years, except for some difficulty in maintaining her weight.

STUDIES OF THE EFFECT OF TETRAETHYLAMMONIUM CHLORIDE ON GASTRIC MOTOR AND SECRETORY FUNCTION IN PATIENTS WITH DUODENAL ULCER*

HIGH S. BROWN, E. LEONARD POSEY, JR., AND EARL E. GAMBILL

A decided reduction in the concentration of free and total acids in the gastric juice followed the intravenous and intramuscular administration of tetraethylammonium chloride. The concentration of free hydrochloric acid was reduced by an average of 62 per cent for thirty to sixty minutes when tetraethylammonium chloride was given intravenously to five patients and by an average of 44 per cent for two to three hours when tetraethylammonium chloride was given intramuscularly to five patients.

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The concentration of chlorides of the gastric juice was reduced by approximately 25 per cent after intravenous or intramuscular injection of tetraethylammonium chloride. We do not know why the reduction in the concentration of chloride was not of the same magnitude as the reduction in gastric acidity.

The intravenous or intramuscular injection of tetraethylammonium chloride resulted in complete cessation of gastric motility for approximately the same length of time as the reduction in gastric acidity.

The pain of ulcer which was present in two cases at the time of injection of tetraethylammonium chloride disappeared simultaneously with the cessation of gastric motility.

The possible therapeutic usefulness of tetraethylammonium chloride is limited because of the relatively short duration of action of the drug and because of untoward side effects. At present its value is largely that of a research tool.

GASTROJEJUNAL ULCER: CLINICAL FEATURES AND LATE RESULTS*

JAMES T. PRIESTLEY AND ROBERT H. GIBSON

The etiology of jejunal ulcer is similar to that of duodenal ulcer. The routine use of gastro-enterostomy in the treatment of duodenal ulcer is followed by a relatively high incidence of jejunal ulcer. Similar use of moderately high gastric resection with complete removal of the pyloric antrum is followed by a low incidence of jejunal ulcer. The ultimate frequency of jejunal ulcer after vagotomy and gastro-enterostomy remains to be determined. Prevention is of paramount importance in any consideration of jejunal ulcer. Diagnosis of this lesion usually is not difficult. The complications are hemorrhage, perforation and gastrojejunal fistula.

Treatment of jejunal ulcer is primarily surgical. To date the best results have been obtained by disconnection of the gastro-enteric stoma, excision of the jejunal ulcer and adequate gastric resection of the posterior Polya type. With this type of treatment results are satisfactory over a period of five to ten years in approximately 87 per cent of patients who have undergone previous gastro-enterostomy. Results are less satisfactory if the original operation was partial gastrectomy. From a physiologic point of view vagotomy would seem to be a sound procedure if the original operation was partial gastrectomy. Late results of vagotomy in the treatment of jejunal ulcer remain to be determined. Of forty-four cases in which this procedure was performed the immediate results have been good in nineteen of twenty-four cases in which vagotomy was performed for jejunal ulcer that developed after partial gastrectomy and in nineteen of twenty cases in which jejunal ulcer developed after gastro-enterostomy.

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A CONSIDERATION OF DUODENAL ULCER*

CHARLES W. MAYO

Some physicians may feel that the subject of duodenal ulcer is a well-worn one. However, to the patient who has a duodenal ulcer, it is not. Members of the medical profession, I may add, are by no means immune to this type of ulcer and, in general, they pay us little attention to the mandates of a good medical regime as do the inattentive patients whom they may treat, or even less.

Duodenal ulcer is an important subject and will continue to be as long as the tempo of life is "stepped up" and the voluntary and forced demands are assumed by persons who should not assume them but whose natures will not permit a less active life. If you want to hire a man who will do more than he is physically capable of doing, hire one with a duodenal ulcer. He was born a production worrier.

There was a period when the diagnosis of duodenal ulcer indicated surgical intervention, with little question. Fortunately for many patients, that time is past. The indications for surgical intervention are much more clear-cut and, likewise, experience has taught us which instances justify medical therapy.

It is not a simple or an easy thing to arrive at an accurate evaluation of any given surgical procedure, nor is it always the rule that a proper evaluation is made of any given medical regime.

Although much essential knowledge has been gained from the fields of experimental medicine and surgery, the final criterion on which the judgment of any technic or therapy must be based is, What is the end result in a given case—whether the patient was surgically or medically treated—not one year later but, rather, ten or twenty years later?

When a physician sees a patient who underwent a posterior gastro-enterostomy twenty-five years previously and who has a gastrojejunal ulcer, he wonders who reported the case in his series of cures following posterior gastro-enterostomy. When a patient presents himself for a cholecystectomy because of attacks of pain from gallstones and it is found that he was seen fifteen years previously because of obstructing duodenal ulcer for which he was advised to submit to surgical treatment but did not, and has done well without losing time from work in the interim, the physician cannot help but reflect and wonder what the result might have been if the patient had submitted to operation.

Posterior gastro-enterostomy is a good operation when properly selected and properly performed for a given condition, for instance, for chronic obstructing duodenal ulcer in a patient more than forty-five years of age, in which case, other factors being equal, it will produce a high percentage of excellent results. However, there are many ways of performing the operation. Among the things to be considered are the position of the new opening on the posterior wall of the stomach, how close or how far it is from the pylorus, how large the opening is, the use of isoperistaltic or antiperistaltic anastomosis and the use of absorbable or nonabsorbable suture material.

* Abridgment of paper read at exercises commemorating the centenary of The Mercy Hospital of Pittsburgh, Pennsylvania, May 10 to 13, 1947.

In a statistical analysis, to see a grouping under one heading, such as "posterior gastro-enterostomy," to me means little unless the operation was done in a particular way, and then I am interested in immediate results and end results over a period of years.

Any surgeon who fails to appreciate the factor of heredity in duodenal ulcer is sadly in error. The tendency for ulcer to occur is more marked in some people than in others. The patient's antecedents are not changed by an operation. The surgeon who tells his patient after any type of operation for duodenal ulcer that he can do anything and can eat or drink anything is doing his patient an injustice and his percentage of failures and of early or late complications will be higher than he knows or higher than he will admit. It should never be forgotten that duodenal ulcer is primarily a medical problem and that it remains so postoperatively.

A comment or two on the latest surgical operation for this condition may not be out of place. This is vagus neurectomy, either alone or in combination with gastro-enterostomy or resection. The role of the vagus nerve in the control of the acidity of the gastric contents long has been known. In the 1920's, an operation was performed which consisted of severing the submucosal branches of the vagus nerve about half the distance around the wall of the stomach, above the angle of the lesser curvature. This procedure reduced the acidity for a period of nine months to a year but hyperacidity then returned. For some years, not much was done as far as the vagus nerve was concerned. Then Dragstedt's work of cutting the right and left vagus nerves above the stomach on the lower portion of the esophagus came to the forefront. The discussion as to the relative values of the transthoracic and abdominal approaches to accomplish this has waxed hot at times since then, as has the discussion regarding the actual and theoretic merits of the operation itself.

It is much too early as yet to know the final answer as to the true part that section of the vagus nerves is to play in the treatment of surgical duodenal ulcer. Some points, however, are worthy of consideration.

First, in some of the cases a test is made a few days after the operation which, at least in some of the instances, is considered proof of whether or not the section has been complete, the test being based on the stimulation of acid formation. Those of us who do thyroid surgery are aware of a temporary postoperative complication known as traumatic recurrent nerve paralysis which develops occasionally. This condition may exist for a period of from several days to two or three months but function of the nerve returns eventually. The same is much more probable as far as some branches of the vagus nerve are concerned, since this nerve could well be injured but not severed during the operation with a resultant paralysis for a prolonged period. The surgeon should not state dictatorially a few days after the operation that the test proved that gastric anacidity existed and that, therefore, complete vagotomy had been performed. The test should not be considered certain proof at any time short of two months from the date of the operation. A review of records later may be misinterpreted unless this thought is kept in mind.

The patient with the more severe type of duodenal ulcer who remains a problem even after operation has been performed has become known as an "ulcer former." In the future, patients who have undergone complete

gastric neurectomy should be watched closely because of the possibility that the creation of a state of anacidity in a chronic "ulcer former" may eventually result in setting the stage for the development of a malignant lesion.

From the medical standpoint, Ivy and his associates and others have used enterogastrone in the treatment of duodenal ulcer. It has potentiality as an adjunct to medical therapy but, as is true of vagus neurectomy, sufficient time has not elapsed to permit an evaluation of its true worth.

You perhaps have seen or heard quoted the facetious remark that the time for surgical intervention in the presence of duodenal ulcer is after nine complete and permanent medical cures have been obtained. The sum and substance of this statement, of course, is that medical treatment of this pathologic process is *not one which can be adhered to today and forgotten tomorrow* but is a continuing regime, the strictness of which must vary in each individual case to achieve optimal results.

When one consults in a case in which the diagnosis of duodenal ulcer has been made and the subject of medical treatment is discussed, there are many considerations that must be kept in mind. If the condition has been of long standing and many medical regimes have been tried, it is important to know in detail of what they consisted and how devoted the patient has been in fulfilling his own obligation to their demands. If the diagnosis has been made for the first time, then the basic philosophy behind the cause and treatment can be initiated directly. In other words, the first duty of the physician is to make sure that the patient knows what condition he has, why he has it, why certain treatment is indicated and why any treatment will fail if instructions are not followed.

All patients cannot be treated alike with equal success. Patients will react differently to treatment. The real basic purpose behind any medical therapy for this type of ulcer is the control of the acidity of the gastric contents. Controlling the acidity will control the ulcer.

Some patients feel that a physician makes a special point of first finding out all the things they like and then telling them to discontinue all of them. Neither moderate smoking nor the use of alcoholic spirits in moderation need be discontinued by every patient who has a duodenal ulcer. Yet, in some instances, the smoking of one cigaret may raise the value for the acidity of the gastric contents forty points, and an alcoholic drink mixed with charged water may cause gastric distress whereas a similar drink mixed with plain water may cause no trouble. Each patient is an individual problem.

One is asked, "Doctor, what can I eat?" or "Doctor, what can't I eat?" The answer is not known, actually. It depends on what distresses the individual patient, that is, on what combination of foods or drinks causes discomfort or pain. Each patient must be a detective in his own case and by constant attention arrive finally at a knowledge of what he can eat, drink and do, and be comfortable, and vice versa. He can be given a basic diet which proves satisfactory for the majority of patients but if something included in such a diet is harmful toward the desired end it must be eliminated and a physician need not necessarily be consulted.

Milk and cream still are firm stand-bys in most medical regimes for duodenal ulcer. However, there are exceptions; they are not "musts" because some patients are, or become, sensitive to milk and cream and they

become allergic to them to such an extent that their continued use actually may be harmful. One patient complained that he had drunk so much milk and cream for so long that the sight of a cow made him nauseated.

Alkalies and certain bases routinely are included in most regimes for duodenal ulcer, at least to tide the patient over an acute episode. This treatment again is in line with the control of the acidity. The uninstructed patients will take a teaspoonful or more of some alkali, put it in a glass and mix it with about a quarter or a third of a glass of water, drink it with a gulp and obtain temporary relief of pain. The stomach, however, immediately rushes out acids to neutralize the alkali and does not stop doing so on completion of neutralization. Again, the acidity becomes high and again the use of alkali is resorted to, and the result is a vicious cycle. Alkali, or any similar medication, never should be taken with less than two full glasses of water.

This brings up one of my favorite subjects in connection with any discussion of duodenal ulcer; namely, the value of water in the treatment of this pathologic condition.

In a former talk on duodenal ulcer in Pittsburgh, what I had to say about water and health evoked the use of some of my statements by advertisers of certain bottled spring waters, to my embarrassment. However, the theory behind the employment of ample water in this condition is dilution rather than neutralization. This is a more logical and certainly a cheaper form of treatment.

The average amount of water taken by the ulcer patient is low. There may be times in the year when it is higher than at other times but usually it is not more than three glassfuls a day. The patient who has a gastrojejunal ulcer usually takes less than two glassfuls of water per day. Careful questioning as to water intake is, I believe, important.

The correction of water intake of a person who for years has had the habit of not taking much has to be accomplished by degrees. The importance of it must be outlined logically and the intake should be increased by having the person drink an additional glass of water a day until a sufficient amount for that person has been determined. It may vary from eight to twelve glassfuls, which includes two glassfuls with each meal. These patients should be instructed not to pass a drinking fountain without taking a few swallows of water. If the person is a salesman or a farmer, he should carry water in a thermos container in his car or to the field. The habit must be developed. Thereafter, the taking of water is easy.

One other point in this regard should be emphasized. The important thing is to drinkable water into the stomach all day long. Drinking large quantities at long intervals does not serve adequately the theory of dilution and this practice will not be as effective as drinking water frequently.

I close with what to me has become an habitual statement; namely, that no medical regime for duodenal ulcer which disregards an adequate intake of water is either efficient or effective. Duodenal ulcer is an individual problem in each case and the medical or surgical treatment must be planned and carried out to suit each person so afflicted. A happy and productive life can be lived by the affected patients if they will live what is a normal life for them.

POSSIBLE RELATION OF DUODENITIS AND DUODENAL ULCER TO HEPATIC CIRRHOSIS*

WILLIAM CARPENTER McCARTY, SR.

Fortunately, and perhaps correctly, we are beginning to speak of chronic hepatitis, an expression which includes the late stages described long before we had opportunities to study the early stages at surgical exploration. Among the many causes of advanced chronic hepatitis, one rarely hears of duodenitis and duodenal ulcers and their possible relation to this condition. As long ago as 1872, 1876, 1882 and 1908, Meyer, Charcot and Gombault, and Maffucci and Tsunoda described, respectively, the experimental production of biliary cirrhosis by artificial stenosis and partial stenosis of the common duct, which is not an uncommon surgical condition produced by duodenal ulcer. Formerly it was thought that most duodenal ulcers were single and near the pylorus; duodenal ulcers are, however, very often multiple and exist just above, at, and just below the papilla of Vater. In these portions of the duodenum it is quite reasonable to think of repeated interference with the patency of both the common bile and pancreatic ducts, thereby producing unfavorable changes in both the liver and the pancreas. From a large series I have chosen two examples of the association of cirrhosis with duodenal ulcers which partially obstructed the common duct.

A male, aged sixty years, was operated upon for cholecystitis. He unproved for five or six months and again had epigastric pains, jaundice, and vomiting. At the second operation, performed seventeen months later, the gallbladder was distended, the common duct dilated, and the head of the pancreas very hard. The patient died on the twelfth day following the re-operation and the necropsy showed a marked chronic hepatitis (called cirrhosis), chronic cholecystitis, chronic pancreatitis, chronic congestion of the spleen, and a chronic ulcer of the duodenum at the papilla of Vater about 1 cm. in diameter. There was almost complete stenosis of the common duct at the base of the ulcer.

A male, aged fifty-eight, had had attacks of severe epigastric pain which extended to the back. At operation one gallstone was removed and the gallbladder was drained. There was a hard mass felt at the end of the common duct, thought clinically to be a carcinoma. The patient died on the fourth postoperative day from hemorrhage into the bowel. At postmortem examination there was a duodenal ulcer 2 cm. in diameter with the common duct running through the base of the ulcer. There was a very definite biliary hepatitis, called "cirrhosis." The surgeon noted that the liver was "angiomatous."

My purpose is merely to stimulate others to watch for this association at autopsy and at surgical exploration. Even experimental production of partial or periodic occlusion of the common duct and pancreatic duct might throw light on some of the diseases of the liver and pancreas which have been considered primary entities rather than sequelae of duodenal pathologic conditions.

* Abstract, published in the *American Journal of Pathology*, 23:897 (Sept.) 1947.

PRESENT STATUS OF SURGICAL TREATMENT OF DUODENAL ULCER*

EDWARD S. JUDD, JR.

Any discussion of surgical treatment of duodenal ulcer in modern times immediately brings to the fore the possibility of resection of the vagus nerve supply to the stomach. Dragstedt and his co-workers have now followed a large series of patients for a long enough time to draw certain definite conclusions and they feel that their hypothetical viewpoint is well justified. As is the case with many new, or at least reintroduced, procedures, perhaps uncritical use of vagotomy by scattered investigators who may or may not be completely qualified may cast some air of pessimism on the results, which tends to cloud the picture. It has been said that vagotomy for duodenal ulcer has reached its crossroads. In the relatively near future, it should be definitely decided whether the operation will become recognized as the best of all possible procedures or will be relegated to treatment of only a small group of patients. In the Mayo Clinic such excellent results have been obtained by time-honored principles of surgical management that a majority of the surgeons prefer to treat complicated duodenal ulcers with means that have proved to be of lasting value. At the same time, close watch is being kept on results reported from other clinics in cases in which vagotomy has been performed and a modified series of vagotomies is being analyzed progressively. It would seem, therefore, to be of the most practical value to consider first those measures which are known to be sound and to finish the discussion with a short appraisal of those factors which must be considered in vagotomy.

INDICATIONS FOR SURGICAL TREATMENT

The indications for surgical treatment of duodenal ulcer are now clear-cut (table 1).

TABLE 1
INDICATIONS FOR SURGICAL TREATMENT
OF DUODENAL ULCER

Primary	Secondary
Obstruction	Economic or social status
Perforation	Repeated dietary and other indiscretions
Hemorrhage	Excessive gastric acidity
Failure of medical management	Long duration of symptoms
Cytologic lesion with possible malignancy	Exceptionally severe symptoms

Of the primary factors perhaps the most important is hemorrhage. This may present itself as an acute episode of massive hemorrhage or as a history of recurrent, rather massive hemorrhages in the past. There is still no great unanimity of opinion on the proper management of acute massive hemorrhage. A rather good working rule in our emergency service has been

* Abridgment of paper published in full in *The Journal of the Kansas Medical Society* 49 1-10 (Jan.) 1948.

that those patients with duodenal ulcer who are less than forty-five years of age frequently may be expected to respond satisfactorily to treatment for massive hemorrhage; however, those who are more than forty-five years of age are observed very closely in this type of complication as the risk of medical management is greatly increased above that point. It is the practice at the clinic to institute medical treatment for at least forty-eight hours in all cases in which bleeding occurs. If there is still evidence of continued or recurrent bleeding, immediate surgical treatment is very seriously considered. If the patient presents himself between hemorrhagic episodes and if there are other factors suggesting complication of the ulcer, one is much more inclined to suggest surgical intervention.

The second important primary complication is obstruction. The obstruction commonly falls into two different classifications: either the acute inflammatory type or the chronic sclerotic type. We are all familiar with the acute type which comes on shortly after the flare-up in the patient's ulcer symptoms. Most of these patients will respond in a short time to intensive medical treatment, which will include either frequent aspiration of the stomach or constant suction through a nasal tube, with either a retention type of liquid diet or a starvation program. Many of these patients will respond so remarkably in ten days or two weeks that they are not interested in any further treatment and they are dismissed to their homes, only to return later with the same problem all over again.

The patient who has the sclerotic type of ulcer presents a less dramatic episode when he is admitted but his history will reveal that the stomach cannot empty properly. There is a great deal of difference in the anatomic appearance of these ulcers, as the subacutely inflamed type is by far the more difficult to handle surgically. If a patient has a chronic obstructing type of duodenal ulcer, all are agreed that there is little to offer aside from surgical management.

Perforation of a duodenal ulcer is obviously an emergency when it is encountered as an acute phenomenon. There is agreement that the simplest most adequate closure of the perforation should be the method of choice. Further procedures during the emergency do not appear to be warranted. Roscoe Graham stated that the opening may be closed with a full omental patch rather than by suturing the defect shut. More extensive surgical procedures should be delayed until later. My colleagues and I do not insist that all patients who have perforated ulcer should return at a later date for radical resection but repeated perforations are commonly seen.

The fourth primary indication for surgical treatment is the intractability of the patient's pain and other symptoms. When a patient has actually tried for a period of several years to follow the diet and all other instructions outlined for him and still finds that he is unable to perform daily work or lesser tasks in a comfortable manner, most physicians will agree that surgical treatment is the best course for him.

Added to this last is a fifth factor, notably any doubt whether the lesion at the outlet of the stomach is benign or malignant. Frequently, an occasion will arise when there is an obstructing lesion at the outlet with only a moderate degree of free acid present and other features which are not particularly helpful in establishing a proper diagnosis. In this type of case, my colleagues and I do not delay long in attempting to clear up the situa-

tion with medical means. All too often a small carcinoma just at the pylorus is known to present symptoms and signs strongly suggestive of duodenal ulcer. In this type of situation, surgical exploration is certainly justified.

Besides these primary considerations, there are certainly secondary factors which must be taken into account. Among these is the economic status of the patient. His primary concern is in making a living and providing for his family. It may be that he is an outstanding man in his own occupation, but that occupation may make certain demands not allowed in a regimen for duodenal ulcer. In such cases, we are more inclined to advise early surgical treatment than when this factor is not present. In a small group of cases there is an inability to co-operate with the physician and, in spite of careful instruction in the dietary regimen, for one reason or another, the regimen cannot be followed so that surgical measures are the only recourse. Then, too, some patients will exhibit an excessive degree of free acid in spite of medical management and it appears that the only way to control this factor is to excise a large share of the acid-producing tissue. A prolonged history of symptoms of duodenal ulcer experienced by a middle-aged patient, when taken into consideration with other factors, usually inclines one toward a decision to advise surgical treatment, as does marked severity of symptoms which may persist in spite of a rather well-ordered life.

TRENDS IN SURGICAL TREATMENT

Figure 17 illustrates the trend of medical versus surgical handling. In 1931, more than 25 per cent of all the patients who had a definite diagnosis underwent surgical treatment. This incidence fell off rather rapidly and

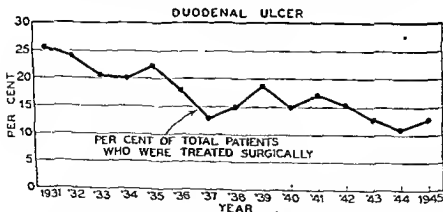


Fig 17—Incidence of surgical treatment for duodenal ulcer.

steadily with only occasional minor variations during the entire fifteen year period. In 1944, it reached perhaps the irreducible minimum of approximately 12 per cent being sent for surgical treatment.

It is of interest to analyze this incidence of the medical treatment further in order to see whether the type of operation being performed had any influence on the decision in the minds of the surgeon and the internist alike.

In 1931, as shown in figure 18, gastro-enterostomy was the operation most frequently performed for duodenal ulcer. It maintained its favor for at least eight years, after which it rather rapidly dropped in incidence. During the same eight years, pyloroplasty was performed rather frequently but then rather suddenly it lost favor and has not been used at all in the past seven years. On the other hand, gastric resection was in its infancy at the

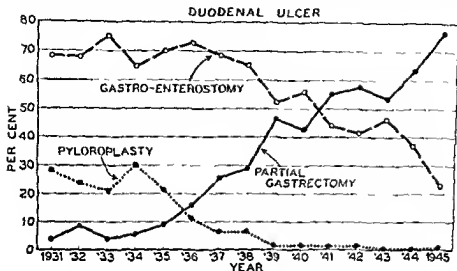


Fig. 18.—Incidence of different surgical procedures for duodenal ulcer

beginning of this same period. It had a rather slow start but after the first seven years it became much more frequently used and climbed steadily and rapidly to equal gastro-enterostomy in 1940. Since that time it has replaced that operation in many instances.

TECHNICAL CONSIDERATIONS

My colleagues and I prefer to attach the jejunum to the posterior wall of the stomach, placing the afferent loop high on the lesser curvature side and directing the stoma obliquely downward and to the left so that the efferent loop reaches from the lowest point just to the left of the angle of the stomach. We prefer posterior gastro-enterostomy because it appears to be much more dependent, a much shorter loop on the afferent side is possible and the postoperative gastric retention seems to be much less of a problem. In performing the anastomosis, the opening should be large enough for proper emptying, it should not be placed too high and the intestine should not be put straight across the stomach. Two rows of sutures are ordinarily adequate but many surgeons prefer three, usually two rows of catgut sutures with an outer row of interrupted silk so that a stricture may not form, as might be the case if a running row of silk were used. It must be remembered that a dilated stomach will shrink to almost normal size and this will tend to make the stoma considerably smaller.

If posterior anastomosis is performed, my colleagues and I are careful to suture the stomach below the incision in the mesocolon for a distance

of at least $\frac{3}{4}$ inch (2 cm.) Improper attention to this detail will result in angulation of the proximal loop of the intestine, which may have a disastrous effect, or it may allow prolapse of another loop with obstruction. In certain cases it will be rather difficult to close the opening completely but it must be accomplished.

It has been acknowledged that anterior gastro-enterostomy is much easier to accomplish than posterior gastro-enterostomy with no danger to the blood vessels in the mesocolon, and, should gastrojejunal ulceration develop later, it is considerably easier to approach the new ulcer to take down the anastomosis. We have not hesitated to employ anterior gastro-enterostomy for markedly obese patients with a high-riding, small stomach and a short, thick mesocolon, but this situation does not occur very often.

Gastro-enterostomy at the present time has by no means been condemned at the clinic. In a very small group of cases it is the operation of choice. In an occasional case, it is the operation of expediency; thus an older patient who is a poor surgical risk, who has a chronic, fibrotic, obstructing duodenal ulcer with a relatively low value for free hydrochloric

TABLE 2
CHOICE OF OPERATION FOR DUODENAL ULCER
Factors favoring

Gastro-enterostomy	Gastric resection
Advanced age	Middle age
Low acids	High acids
No gastritis	Severe gastritis
Chronic lesion	Subacute lesion
Obstruction	Obstruction (optional)
Poor surgical risk	Good surgical risk
Minimal neurogenic factor	Marked neurogenic factor
Single ulcer	Multiple ulcers

acid, in whom we are certain there is not a carcinoma of the pylorus and who is not a high-strung, emotionally unstable individual may well benefit by gastro-enterostomy (table 2). Occasionally one encounters a situation in which a satisfactory closure of the duodenal stump would be very questionable because of the inflammation or would definitely be hazardous because of the proximity to the ampulla or common bile duct. Gastro-enterostomy is occasionally still done in this type of a case.

The more or less standard procedure at the present time in many clinics is subtotal gastrectomy. The purpose of the operation is obviously, first of all, to remove a large share of the acid-producing tissue. Another reason for performing subtotal gastrectomy is to provide a new opening to restore gastro-intestinal function. It has been our experience that retention is less common and much less severe after gastric resection than might be the case if gastro-enterostomy had been performed. There is a resultant reduction in the capacity of the stomach and obviously there will be a great change in the physiologic aspects as well as the anatomic ones. Critics state that this small gastric pouch may produce untoward symptoms after the operation. An occasional patient is observed who has what is known as the "dumping" syndrome because the stomach empties so rapidly. I believe that this

phenomenon is being observed less frequently than previously but it still should be kept in mind.

There are many modifications of gastric resection but the one most commonly performed is that known as the "posterior Polya" type. At least the lower two thirds of the stomach and occasionally the lower three fourths are resected. The danger point of the operation is in the inversion of the duodenal stump. In the highly inflamed duodenal tissue it is occasionally difficult to obtain a satisfactory closure. Frequently by doing the so-called open procedure in which no clamps are placed across the duodenum, a good inversion can first be obtained by the Connell suture without crushing any of the tissue. This can be reinforced by two rows of sutures, the last turning the stump to the pancreatic capsule, and then the stump can be covered with an omental pad. The surgeon is ever on the alert for the common bile duct, especially in cases in which there is much inflammation and considerable foreshortening of the first duodenal segment. In such cases the distance from the ampulla, which we have found normally to average 8 cm., may be shortened to 4 cm. or less. One other point of caution concerns the patient who has had pyloroplasty in the past. The pyloroplasty will have removed the pylorus and a variable amount of duodenal tissue. Cases are on record in which the common bile duct has been inverted or injured because this fact was not kept in mind.

The Polya procedure employs the entire width of the stomach in the anastomosis whereas the Hofmeister procedure closes the lesser curvature side, allows high resection on that side and permits a smaller anastomosis. The immediate result of this is that the anastomosis can be performed with better exposure, as one is working in the center of the surgical field, with the lesser curvature already secure. A word of caution here reminds one that the esophagus frequently comes in at what appears to be a low point because the fundus of the stomach extends so high above the esophageal junction. Cases are on record in which the esophagus has been sutured shut from below by high application of clamps in attempting to perform the Hofmeister procedure.

Recently it has been the conclusion among many of our surgeons that the actual removal of the duodenal ulcer is not as important as was once thought. Many cases have been described in which the ulcer has perforated or penetrated into the pancreas and the duodenum has been closed just proximal to this point, the ulcer not being removed. Subsequent examination has revealed that the ulcer has completely healed. Scattered reports from other clinics indicating severe injury to the ampulla of the common bile duct produced by attempting to excise a duodenal ulcer have led many surgeons to the logical conclusion that the removal of the ulcer is not worth what little additional protection might be gained.

At the Mayo Clinic, Priestley and Clagett have done several large series of gastric resections for duodenal ulcers, completing the operations as Billroth I procedures. They both feel that this is a highly satisfactory operation. It presupposes that the patient has an ulcer which can be removed and still leave enough normal duodenal tissue for a good anastomosis. The patient must have enough mobilizable duodenum so that adequate resection of gastric tissue can still be carried out without placing tension on the anastomosis. Certainly far less surgical manipulation is necessary than in per-

forming a Polya or Hofmeister operation, there is no threat to the mesocolon and no decision needs to be made whether the anastomosis is to be posterior or anterior. Priestley and Clagett point out also that there will be no anastomotic jejunal ulcer, that the duodenum is more resistant than the jejunum to recurrent ulceration and that should there be a recurrence, the patient is no worse off than prior to the Billroth I type of anastomosis.

VAGOTOMY

It has been aptly stated that vagotomy today has arrived at the crossroads. In the relatively near future it is anticipated that the operation either will be extended to a large group of patients and will continue to be described in enthusiastic terms or will be relegated to a somewhat narrowed field.

Dragstedt has emphasized that the success of the operation is based on complete resection of the vagus nerves to abolish the psychic phase of gastric secretion and perhaps other neurogenic influences on the gastric mucosa. He has pointed out the evidence accumulated by Cushing, who reported an increased occurrence of acute perforating ulcer of the stomach and duodenum in certain patients suffering from lesions of the brain. Perhaps the most significant features stressed by Dragstedt are that gastric hypermotility has been a marked feature in most cases of ulcer and that there is an excessive secretion of gastric juice occurring in an empty stomach in the absence of the usual stimulus of food. Complete section of the vagus nerves will remove both of these factors. It is pointed out that after vagotomy, the same type of ulcer pain previously noted can be produced again by administering hydrochloric acid to the patient. In Dragstedt's opinion this shows that the relief of the pain is not due to interruption of the sensory fibers. It is now widely corroborated that healing of a large ulcer crater will frequently be shown by microscopic and roentgenographic evidence after this type of operation. Dragstedt further has stated that excessive secretion of the gastric juices occurring in the empty stomach without a buffering effect of food and the neutralizing elements from duodenal secretion will obviously have much higher chance of producing ulceration.

The time-honored operations for duodenal ulcer have now had at least fifteen years for evaluation but the ultimate conclusion concerning vagotomy rests now only with the test of time. One frequently reads, especially in the reports from older, more experienced surgeons, that now operations are to be considered in the light of many which have been discarded. A prime example of this is total thyroidectomy, formerly done in the treatment of certain types of heart disease.

An attempt to reach a uniform conclusion concerning vagotomy today that would apply to many different clinics and centers ends only in confusion. At the present time, the definite indications for vagotomy will vary with the surgeons who are performing the operation for duodenal ulcer. The large majority of surgeons who have mastered the technique and all of the factors in performing gastric resection are still somewhat reluctant to attempt vagotomy widely. They feel that they now have the means at their disposal for control of ulcer in a relatively large number of patients and they continue to perform wide resection. At the same time, they are care-

fully evaluating all reports from surgeons who are interested in developing the field of vagotomy. The outstanding impression that is left with one after surveying the literature is that, before a definite conclusion is reached, this field should be evaluated further by men such as Dragstedt and others who have done such commendable work in it. The argument about supra-diaphragmatic versus infradiaphragmatic interruption of the vagus nerves probably will continue for the present.

Walters and his associates felt that the most thorough knowledge of the anatomy of the vagus nerves just below the diaphragm is indicated, therefore, they performed dissections in more than 100 cases at necropsy. Their conclusion is that in more than 90 per cent of the cases, the infradiaphragmatic approach permits almost as perfect a division of all of the vagus nerve supply as does the transthoracic approach. In less than 10 per cent of the subjects, the exact anatomic distribution of the nerve fibers was inconstant and in a few of the subjects there was no one well-developed trunk on one or on both sides of the esophagus and the vagus nerve supply was distributed through many small branches. It is in the latter type of case that the surgeon would probably realize a less perfect result in attempting to interrupt the entire vagus nerve supply.

Taking the other viewpoint are Moore and his group in Boston. In their report, all of the patients who had duodenal ulcer had undergone transthoracic vagotomy. It was felt that a much more complete division of the nerves was possible in this way. Their results are carefully and critically classified. It was noted that even in the cases in which satisfactory results were obtained, there were occasional gastro-intestinal symptoms. Some of these were transient but the patients were concerned enough about them that from that standpoint the immediate postoperative results were a little short of what they had expected.

All of the investigators urge that anyone attempting to do a series of these operations with whatever approach, should check the results by means of the insulin test. The response of the level of gastric acidity to hypoglycemia produced by intravenous injection of 20 to 25 units of insulin is definitely abnormal in cases of duodenal ulcer. This test is not without its own severe effects and actually can be dangerous if it is not completely controlled at all times. Studies of blood sugar levels must be made and all of the facilities for the immediate intravenous injection of solution of glucose must be available.

The criterion for the proper performance of complete bilateral vagotomy is the abolition of the gastric acid response to the hypoglycemia produced by this intravenously administered dose of insulin. Any tendency toward abnormal response suggests that there are still some fibers of vagus nerves remaining intact. Studies of gastric motility have been made employing intragastric balloons and kymographic tracings. Moore and others feel that the gastric stasis is overcome within nine months although delay in the emptying of the stomach may persist. In addition to the test for suggestive pain which is demonstrated by the introduction of hydrochloric acid into the vagotomized stomach, it is possible to produce gastric pain by over-distention of the balloon, which once again produces symptoms showing that the result of the operation is not contingent on relief of pain alone.

If one is deciding which procedure to employ in the surgical management

of duodenal ulcer, he still must keep in mind that his criterion is going to be the best surgical result which he personally can produce (table 3). At the present time our choice of operation at the clinic still favors wide gastric resection in those cases in which there are definitely one or more clear-cut indications for surgical intervention.

Here it must be emphasized that in the past not enough practical psychologic analyses have been available to the surgeon at all times. As Dragstedt pointed out earlier and as other surgeons have re-emphasized, patients in the past have been considered either candidates for the psychiatric service in the hospital or else strictly surgical problems. It becomes more and more apparent that in many of those cases in which the result after surgical treatment is considered a failure one can look back with the wish that complete psychiatric investigation had been performed before surgical intervention. A very important point for the surgeon to establish in his own investigation is whether the so-called intractable pain with which the patient presents himself is actually pain produced by the ulcer itself. It has been our experience that ulcer pain, no matter how intense and no matter of how long duration, can usually be controlled, if only for a very short time, by extensive medical measures in the hospital. If the

TABLE 3
SOME FACTORS WHICH INFLUENCE CHOICE
OF OPERATION FOR DUODENAL ULCER

Race	Severity of symptoms
Sex	Gastric acidity
Age	Roentgenologic evidence
Occupation	Gastritis
Economic status	Local nature of lesion
Personal habits	Multiplicity of lesions
Type of symptoms	Difficulty of operation

patient has some bizarre tendencies in his pain pattern or some slight suggestion of psychologic imbalance, it would be well worth while to defer any further thought of surgical intervention until all of these factors have been properly evaluated. All too often, one sees a patient who apparently has withstood a fairly large surgical procedure, and from all anatomic standpoints, the operation has been successful, but the patient still experiences the same type of pain he has had for years. In any conclusion concerning any type of surgical procedure, the results will be clouded if any of the unstable or psychologically unbalanced patients are included, no matter which way the results appear to point.

Being confronted then by a patient who definitely presents several of the primary indications for some type of surgical intervention, one will constantly be questioned concerning the new "nerve operation." Several of the surgeons in the clinic at the present moment feel that the indications for vagotomy become more definite when there is nothing else which will assure a good result in the patient. An example of this type of condition is a young person, especially a male patient less than thirty years of age, who is obviously a high-strung type of individual, working at all times under a great degree of tension; analysis of whose gastric contents reveals high acidity, and whose pain is so intractable that he cannot perform his

usual work properly and perhaps is comfortable only when he is under medical supervision in a hospital. Added to this, he will probably have a long history of ulcer distress in spite of his relative youth. This narrows the field down at the present time to a relatively small group of patients. In the hypothetical case just cited, obviously that type of man represents a group who may have further difficulty even after a rather wide gastric resection and who most certainly would have difficulty after gastroenterostomy alone.

It seems to me that the indication for vagotomy appears at the moment to be rather limited. At the present time, transthoracic vagotomy is being performed occasionally at the clinic for those patients who have undergone adequate gastric resection previously and who have had further ulceration in the jejunum. Walters has been vitally interested in this topic and his indications will necessarily be different from those that others might have. His approach has been mentioned as the subdiaphragmatic and vagotomy is frequently combined with some other type of procedure. However, Walters re-emphasizes that the exact nature of the lesion must be determined in any case and that an obstructive type of lesion at the outlet of the stomach most certainly will require some type of further surgical intervention even though this lesion is proved to be benign. The surgeons at the clinic feel that evidence of pyloric obstruction, whether clinical or roentgenologic, contraindicates the performance of vagotomy alone. Those patients who have come to the clinic after the performance of vagotomy and have presented further symptoms are occasionally found to give positive response to the insulin test; in other words, in a few cases it has been felt that an incomplete vagotomy has been performed. Obviously, these patients will not be criteria for any conclusions concerning vagotomy.

CONCLUSIONS

From my own present standpoint, therefore, my conclusions at the moment must be that a duodenal ulcer is strictly a medical problem until proved otherwise but that, in perhaps 12 per cent of the cases in which the diagnosis of duodenal ulcer has been accomplished, medical measures will not be completely satisfactory. One or more of the now well-established primary and secondary indications will be adequate reason for surgical intervention. When confronted with a complicated duodenal ulcer which requires surgical management, I have felt that, for young, active ulcer patients who have a high degree of free acid, the operation of choice is an adequate gastric resection, usually completed as a Polya anastomosis or a Hofmeister modification of it. All of these patients are tested by analysis of gastric contents after operation and the degree of immediate anacidity has been most encouraging. The anacidity persists for at least four years in more than 80 per cent of the cases. A low concentration of free hydrochloric acid has been noticed in perhaps 20 per cent of the cases.

In dealing with the duodenal stump, the Bancroft modification need be employed only rarely but at present it appears to be a good alternative, to be kept in mind.

The final thought that I have is that a more nearly complete and a more practical psychologic approach to the patient who has complicated duodenal ulcer will probably insure a higher percentage of cures.

ACUTE HEPATITIS: NOTES ON VIRAL AND OTHER TYPES*

GEORGE B. EUSTERMAN

To the physician familiar with acute hepatitis as it occurs in civilian practice, it should be readily apparent that the medical officer in the armed forces, with few exceptions, has a less difficult problem than the civilian physician. As pointed out by Hoagland and Shank, the relatively high incidence of hepatitis of epidemic nature and the relative infrequency of obstructive, chronic degenerative and neoplastic lesions of the biliary tract in men of military age, who were free from all evidences of chronic ill health and physical disability prior to induction, offered favorable circumstances for correct clinical diagnosis.

In order to illustrate the greater complexity of the problem from the civilian standpoint, I reviewed data on 100 consecutive cases of acute hepatitis in which the diagnosis was unequivocal and in which all but one of the patients were jaundiced. These data illustrated the fact that a variety of clinical types is encountered, the differentiation of which may be exceedingly difficult, in fact impossible at times, in the absence of a serologic or other specific diagnostic test for infectious hepatitis. Of course, to less extent the toxic, bacterial, spirochetal and protozoal forms were also encountered in military practice during World War II. In many cases these were associated with so-called tropical diseases such as malaria and amebiasis or resulted from familiar hepatotoxins such as the arsenical compounds and alcohol.

This review also revealed what had been expected; namely, a preponderance of patients with infectious hepatitis, comprising 74 per cent of the total. Also noted was the preponderance of men, constituting 70 per cent, even though most authorities, notably Blumer, consider infectious hepatitis a disease of adolescence attacking both sexes equally. Reports covering recent epidemics of the disease in the civilian population in several of our states confirm Blumer's observations.

The hepatotoxins which figured most prominently in the series of sixteen cases of toxic hepatitis were cinchophen (four), alcohol (four), miscellaneous pharmaceutical products (five), and arsphenamine and hyperthyroid crises (one each). In one instance the cause was undetermined. In the bacterial group, consisting of nine cases, four were the result of septic states, two in association with chronic ulcerative colitis, one each as the result of scarlet fever and pneumonia, and one represented a case of intercurrent hepatitis with jaundice in which the patient had subclinical latent stones in the gallbladder and common duct. The most interesting case in the septic group was one of fatal brucellosis septicemia in association with mitral ulcerative endocarditis due to the same organism as that causing the systemic infection.

Perhaps the most disconcerting factor is the age incidence. Forty-four of seventy-four patients who had infectious hepatitis, almost 60 per cent, were more than thirty years of age. This relatively advanced age also characterized the other groups: the average age of the patients who had toxic hepatitis was forty-two years and that of the patients who had bacterial

* Abstract of paper submitted to *Acta medica Scandinavica*.

hepatitis, omitting one infant two months of age, was forty years. As two thirds of the patients reported by Bloomfield were between thirty-one and fifty years of age, he concluded that acute hepatitis is not necessarily a disease of young adults. I use the expression "disconcerting" in the sense that in view of the age incidence the numerous possibilities of etiologic factors of jaundice are greatly enhanced, thus increasing the diagnostic difficulties.

With further respect to diagnosis under the circumstances of civilian practice infectious hepatitis is rarely recognized in the preicteric stage. The sporadic occurrence which characterizes the large majority of cases is considerable extenuation of lapse in this respect. In this stage the diagnosis is usually that of "influenza," often "intestinal influenza," acute upper respiratory infection, atypical pneumonia, infectious mononucleosis or fever of obscure origin. The symptoms and signs of major importance in diagnosis in this stage appeared to be anorexia, abdominal discomfort, with or without hepatic enlargement and tenderness, absence of leukocytosis and evidence of hepatic damage as revealed by the laboratory procedures that I have discussed.

Once jaundice supervenes, the diagnosis is apparent, especially if the patient is young and if abdominal pain or discomfort has been absent or inconsequential. On the other hand, with the appearance of jaundice, irrespective of the age of the patient, there is a ready tendency in some quarters to look on the condition as surgical, especially if the patient is elderly and has experienced some abdominal pain or discomfort which may be localized to the right upper quadrant of the abdomen. Such distressing abdominal manifestations are not incompatible with acute inflammatory states of the liver as well as with chronic hepatitis and cirrhosis. One may be further misled by the results of cholecystographic examination. As false positive findings are the rule in the presence of any appreciable jaundice, such examination should be postponed until the jaundice disappears.

In my experience the three most important factors to exclude in the average sporadic case of infectious hepatitis, especially in the absence of classic clinical manifestations, are intercurrent acute hepatitis in association with hepatic cirrhosis, obstructive jaundice of malignant origin, especially when an elderly patient is concerned, and infrequently an intercurrent hepatitis with jaundice in a case in which latent stones are present in the gallbladder or ducts, or both. Under such circumstances a detailed case history, careful physical examination, certain tests of hepatic function and observation in the hospital, coupled with the all-important clarifying element of time, usually make possible a successful differential diagnosis. The importance of accurate diagnosis under the circumstances cannot be overemphasized, for a patient who has acute hepatitis, of whatever nature, is a poor surgical risk and in the debatable case it behooves one to give him the benefit of the doubt. In "surgical" jaundice of benign nature (stones, stricture) in the absence of frank evidence of suppurative cholangitis, a reasonable delay, during which time the integrity of the liver may be enhanced by proper measures, is justifiable whether operation is eventually performed or not. In obstructive jaundice of malignant nature the eventual outlook in the large majority of cases is precarious anyway, although in recent years some improvement of prognosis has been made.

To differentiate obstructive jaundice, especially that of malignant origin, from intrahepatic jaundice, one frequently resorts to duodenal intubation. This procedure, sometimes repeated, coupled with a quantitative determination of excretion of urobilinogen in the urine and feces, often proves decisive in differentiating an intrahepatic jaundice from an obstructive one. A persistently high level of serum bilirubin and a prolonged prothrombin time (Quick), not responsive to adequate vitamin K therapy, justify a guarded prognosis. Such signs, along with a low output of hippuric acid, coupled with decreasing concentrations of cholesterol and esters, are often premonitory of impending hepatic coma, and death from acute yellow atrophy supervenes sooner or later.

In the entire series of 100 cases the number of deaths was eight, or 8 per cent. As was to be expected, the mortality rate was greatest in what I regarded as the nonviral, bacterial group. Necropsy routinely revealed massive acute necrosis, that is, acute yellow atrophy of the liver. Five of the female patients, four of them having infectious hepatitis, were afflicted during the parturient period. However, there were no deaths in this group. The high mortality rate which characterizes the various forms of acute nephritis encountered in civilian practice, in contrast to the low death rate in epidemic hepatitis, has been observed by others.

ACUTE OBSTRUCTIVE CHOLECYSTITIS*

PAUL C. KIERNAN

The records of 102 cases of acute obstructive cholecystitis encountered in a five year period were studied. The over-all mortality rate was 3.9 per cent, 1.1 per cent in the group in which surgical treatment was given and 20 per cent in the group in which surgical treatment was not given. Seventy-three and five tenths per cent of the patients gave a history of previous biliary colics and indigestion. Fifty-four of the patients were males and 48 were females. Fifty-seven per cent of the patients were more than fifty years of age. Significant fever (temperature: 101° F. or more) was present in one third and leukocytosis (leukocyte count: 10,000 or more per cubic millimeter of blood) in two thirds of the cases. In 61.5 per cent of the cases in which the gallbladder was gangrenous and 40.9 per cent of those in which it was perforated, the temperature was less than 101° F. and a practically normal leukocyte count was found in 23.1 per cent of the cases in which the gallbladder was gangrenous and 18.2 per cent of those in which it was perforated. Jaundice was present in 19.6 per cent of the cases when the patients were admitted. Palpable gallbladders were noted in 43 per cent. Acute pancreatitis was present in four cases.

In the eighty-seven cases in which surgical treatment was given cholecystectomy was performed in sixty-eight and cholecystostomy in nineteen.

* Abstract of paper read at the meeting of the State Medical Society of Wisconsin, Milwaukee, Wisconsin, October 6 to 8, 1947

Cholecholestomy was performed in fourteen of the twenty cases in which jaundice was present and one or more stones were removed from the common duct in 64 per cent. In the eighty-seven cases in which surgical treatment was given, plus three in which the patient died before surgical treatment could be given, stones were present in 93.5 per cent. There was no correlation between the operative procedure and the duration of the disease. The incidence of gangrene and perforation was twice and three times as great respectively in the cases in which surgical treatment was delayed as in those in which it was given early. In seven cases postoperative complications occurred; none of the patients died.

CONCLUSIONS

1. The risks of acute obstructive cholecystitis would be minimized by proper treatment (operation) in all cases of chronic calculous cholecystitis regardless of the patient's age, excepting only those cases in which operation is contraindicated because of the presence of some other condition which makes the surgical risk greater than the risk resulting from the presence of cholecystic disease.

2. There may be little correlation between the physical signs and the pathologic findings in acute gangrenous perforating cholecystitis.

3. Early operation is the treatment of choice but individualized consideration must be exercised in the proper evaluation of the patient's condition and care of the complicating factors in preparation for surgical treatment.

4. The question of whether cholecystectomy or cholecystostomy should be performed should be decided on the basis of the limitations of the surgeon and the condition of the patient.

SURGICAL TREATMENT OF ACUTE CHOLECYSTITIS*

EDWARD S. JUDD, Jr

A study of the modern literature reveals a definite trend toward a much more active type of treatment in cases of acute cholecystitis with or without stones. As is the situation with many procedures, enthusiasm is likely to lead to overindulgence and scattered reports suggest that perhaps the pendulum has swung too far, and that more radical measures have been employed in certain cases in which conservative measures would have given better results.

The disease is fairly clear-cut and the diagnosis can be made without undue difficulty in the majority of cases. However, some of the more reliable authorities have recommended a great degree of individualization in the selection of treatment. Heuer recalled that in approximately 1910 his chief, the incomparable Halsted, proceeded with cholecystectomy in a

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case of obvious acute cholecystitis. This event made a lasting impression on Heuer and his colleagues and as the years progressed, Heuer became perhaps the outstanding champion of earlier cholecystectomy in cases of this type. His results have been excellent and have pointed the way to his students so that in the particular center where Heuer works early cholecystectomy is the usual treatment for acute cholecystitis. However, Heuer's pupils insist that the decision to perform cholecystectomy must be made for each patient alone and that no arbitrary category should be established.

TREATMENT IN MAYO CLINIC SERIES WITH COMMENTS ON PERFORATION AND GANGRENE

Root and Priestley analyzed the records of 127 patients who had acute cholecystitis and who were observed in the years 1936 through 1942. They concluded that it was very difficult to correlate the pathologic findings with the symptoms presented by the patient. They observed that the incidence of gangrene and perforation obviously increased with the greater duration of the disease. They found that cholecystectomy would be more satisfactory for a great majority of patients within the first seventy-two hours after the actual onset of the symptoms than at any subsequent time before the acute process had actually "cooled off."

Kiernan reviewed the actual data on a series of 102 cases of acute obstructive cholecystitis in which treatment was carried out at the Mayo Clinic in the years 1942 through 1946. Cholecystectomy was performed in sixty-eight cases with one hospital death; cholecystostomy in nineteen cases with no deaths and no surgical treatment was instituted in fifteen cases and three deaths occurred. In twenty-eight of the eighty-seven surgical cases surgical treatment was instituted immediately; in eleven it was carried out early, that is within the first twenty-four to forty-eight hours after onset of the attack, and in forty-eight, treatment was delayed one week or more.

All of the surgeons who perform emergency operations at the clinic had been impressed immediately after the peritoneum is incised with the severity of the condition which is encountered in cases of acute cholecystitis. Rather loose thinking in the past had led general practitioners, as well as some specialists, to tell patients that they need not fear rupture of the gallbladder, as the mechanism is not similar to that in appendicitis. I believe that all surgeons now take a rather contrary view. Rupture of the gallbladder is not only more common than was previously supposed, but should be feared greatly. Gangrenous cholecystitis can be treated surgically with low risk, but the perforated gallbladder presents a different problem. Kiernan listed the cases in his series in which gangrene or perforation was discovered. The incidence of gangrene was twice as high and that of perforation more than three times as high in cases in which operation was delayed as in cases in which it was performed early.

The type of perforation which actually existed is important to surgeons who treat such patients. Any surgeon will encounter a degree of perforation from time to time which had not been suspected before operation. Patients with minimal symptoms, who undergo what might be considered a fairly routine cholecystectomy often are found to have at least impending rupture

of the gallbladder against the colon, duodenum, liver or omentum. It is the perforation into the peritoneal cavity itself which would naturally be expected to give the least favorable prognosis.

Perforation or impending perforation was noted by Kiernan in twenty-two of ninety cases in which pathologic examination of the gallbladder was carried out. Acute free perforation occurred in five cases with three deaths, subacute perforation with pericholecystic abscess in twelve, perforation into a viscus in two and an impending fistula in three.

Following the analysis of the series of cases, Kiernan was struck by the clinical course of four of the patients who did not have gallstones in the entrance of the cystic duct or in the cystic duct itself. Two of these patients apparently suffered from acute obstructive cholecystitis because of obstruction of the ampulla of Vater. One of these patients had carcinoma of the head of the pancreas and the other a stone impacted in the ampulla. In a third case, the only explanation for the obstruction appeared to be extreme inflammation in the cystic duct itself. The reason for this had not been discovered but Kiernan was certain that there was no stone present. In the fourth case, the obstruction was apparently due to pancreatitis. Although no stones were present, there was considerable inflammatory reaction in the cystic duct itself, which apparently had been set off by the inflammation within the pancreas.

SURGICAL METHODS EMPLOYED AT THE MAYO CLINIC

In our practice at the Mayo Clinic when a diagnosis of acute cholecystitis is made, if there are no serious contraindications, the patient is treated surgically. Operation is undertaken at the earliest convenient time which is in the best interest of the patient. This means that haste is not a factor and that sufficient time is allowed to establish a proper fluid balance, to institute decompression by means of a nasal tube and for the clinician and surgeon to have a correct idea of the laboratory findings. At operation, local anesthesia has not been used extensively except in the extreme cases in which no other procedure aside from local drainage is contemplated. On patients who are prepared properly, the most complete operations possible are done and for that reason general anesthesia is used. Occasionally, spinal anesthesia is employed, but this has not been as satisfactory as general anesthesia because of the height of the incision. The decision as to what procedure will be employed is made only after evaluation of the situation after the peritoneum is opened.

The appearance of the gallbladder that the surgeon hopes to find is one of early inflammatory change with perhaps rather marked edema, but with the structures still recognizable after minimal dissection. In fact, in the ideal case, cholecystectomy may be easy as a minimal amount of edema allows dissection of the cystic duct and artery and easy excision of the gallbladder from its bed. In a case of this type, cholecystectomy is certainly the operation of choice.

However, all too often the surgeon is faced with an extreme degree of inflammation in which the omentum is completely wrapped about the gallbladder, and the gentlest dissection is attended by release of fluid from the edematous tissue. Frequently, the transverse colon is caught against the fundus of the gallbladder. There may be an impending or actual fistula

into the duodenum or colon. In such a situation, it may be difficult to tell where liver tissue leaves off and gallbladder tissue starts. What would normally appear to be a thin, pliable free edge of duodenohepatic ligament has been replaced by a thick woody indurated mass measuring 2 to 3 inches (about 5 to 7.6 cm.) across. To attempt to locate the cystic duct and cystic artery in such circumstances might lead to nothing but disaster. Perhaps in an occasional case the cystic duct could be cut long, and the cystic artery could be secured at a level which is still safe, but more often profuse hemorrhage would occur and the control of this might necessitate passing a ligature about the hepatic artery or the common duct or both.

It so happens that at the Mayo Clinic, most of the surgeons have made a habit of performing cholecystectomy from below upward. In cases of acute cholecystitis occasionally they reverse the procedure and start at the fundus. Although in some instances there is considerable bleeding for a time, the vital structures can be identified in this way and cholecystectomy can be accomplished.

Advice of widely experienced surgeons makes the young surgeon hesitate to be bold in cases of acute cholecystitis. On the emergency service at the clinic cholecystostomy is performed if exact identification of structures is difficult. The gallbladder is emptied of its pus or infected bile by trocar. Stones are removed and a finger can be inserted in an attempt to remove all of the stones from the cystic duct. However, prolonged effort is not warranted as the gallbladder can be perforated easily with undue manipulation. In a case of this type, a dressed tube is sutured into the fundus with three purse-string sutures, is brought out through a tunnel in the omentum, and the gallbladder is approximated as nearly as possible to the peritoneum. It is preferable to employ a stah wound for the tube and Penrose drains are inserted beside the gallbladder. Sulfonamides are employed intraperitoneally and penicillin is administered immediately after the patient is returned to bed. The amount of bile that drains from the tube varies widely. Usually there will be bloody bile for the first several days, but this frequently diminishes until the tube drains very little.

The anchoring sutures are removed from the skin and the tube is allowed to drop out when it will; usually this occurs about the fourteenth or fifteenth day. It is surprising how quickly many of these extremely ill patients recover and it has been our experience that for more than 70 per cent no further operation is required; in the remaining 30 per cent the symptoms have varied from very mild pain to frank gallstone colic. We do not hesitate to perform cholecystectomy at a proper interval after cholecystostomy if this is necessary. Minor symptoms in the form of occasional drainage of watery material from the site of the tube have been a nuisance factor. If we do undertake cholecystectomy later, we allow a period of at least six months and preferably longer unless the symptoms are so severe that we must proceed sooner.

We have employed partial cholecystectomy in a number of cases of acute cholecystitis. This operation is an old one and has been called to our attention by Estes. The technic is exactly like that for cholecystostomy, but instead of suturing the "dressed" tube in place, the fundus is incised widely down to a point 1 to 2 cm. from the cystic duct. The resulting flaps of gallbladder are cut away close to the liver. The remaining gallbladder

is dried with gauze and swabbed with tincture of iodine. This procedure removes all remaining mucosa. The distinct advantage of this operation is that the surgeon can work directly on the entrance of the cystic duct and usually remove all of the stones. There is rather brisk bleeding which is controlled by running interlocking sutures near the cut edges of the gallbladder. A plain catheter can be laid in place, with its tip directly in the cystic duct and two or three cigarette drains are laid in the bed of the gallbladder. Preferably these are brought out through a stab wound. The incidence of secondary surgery after partial cholecystectomy is considerably lower than after cholecystostomy. I believe this operation should be kept in mind and should be performed more often than it is at present.

JAUNDICE

A word should be said about jaundice in cases of acute cholecystitis. Ordinarily, the jaundice is due to the presence of calculi within the common duct. However, jaundice may be seen because of extreme cholangitis. Obviously, a severe degree of pancreatitis also will produce it. It is preferred when possible to explore the common duct in these acute cases, but experience has shown that this should not be attempted if there is extreme distortion of the duodenohepatic ligament. It is far better to consider the first operation as merely the first stage. The second stage consists of cholecystectomy and choledochostomy with the relief of obstructive jaundice. It is surprising how many patients become free of jaundice after the first operation and never exhibit jaundice again, indicating that there probably were no stones in the common duct at the first attack. Even the experienced surgeon should not hesitate to temporize by performing cholecystostomy or in selected cases partial cholecystectomy, if doubt exists whether vital structures can be exposed properly.

It is worth while to re-emphasize the now well-established fact that the patient suffering from acute cholecystitis, either with or without stones, must be considered as an individual problem. Whether immediate surgical treatment should be instituted or a period of observation is indicated must be decided on the merits in each case. If surgical treatment is instituted, the operation cannot be selected until the abdomen is opened and the gallbladder is under direct vision.

RECENT ADVANCES IN HEPATIC AND BILIARY DISEASE*

ALBERT M. SNELL

From a review of the advances which have been made in the knowledge of hepatic and biliary disease during the war years, it is apparent that significant progress has been made in a number of important fields. Some of these advances are of unusual clinical interest. Although many others are of equal basic importance, it is the purpose of this paper to confine the

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discussion to those which have a direct bearing on clinical practice at present. Three subjects will be considered: (1) the recent world-wide epidemic of infectious (viral) hepatitis, its sequelae and the implications for the future, (2) observations on atrophic cirrhosis of the liver with particular reference to some of its obscure clinical manifestations and (3) operations for carcinoma of the pancreas with especial reference to the necessity for early diagnosis.

EPIDEMIC HEPATITIS

While sporadic outbreaks of infectious hepatitis have been observed for many years, most major epidemics have been associated with wars and the assembling of armies. The term "campaign jaundice" which appears in numerous British medical writings attests to this fact. World War II was attended by the most widespread epidemic on record. Probably more than 200,000 individuals in military service had the disease in one of its various forms and there are on record large groups of carefully studied cases. Curiously enough it was essentially a disease of land-based forces; the disease rather rarely occurred on shipboard. The early distribution of cases suggested that the disease might well be transmitted by water or food; transmission by insects in some areas has not yet been entirely excluded.

During the period from 1942 to 1945, much was learned about the pathology and physiology of the liver in relation to infectious hepatitis, and also about the clinical syndrome which in its milder aspects differed in no essential particular from that of the well-known catarrhal jaundice. As will appear in the following paragraphs, so favorable a course was not pursued in all cases and the disease was in general of greater severity than catarrhal jaundice and carried with it a distinct mortality rate and considerable morbidity.

Experiments on the transmission of the disease and epidemiologic studies soon established the fact that the etiologic agent was a virus. The tests which were most likely to give positive results long after the disease had passed were those which had to do with alterations in the plasma proteins, the thymol turbidity test being particularly significant in this respect.

The by-products of the epidemic are now of particular concern because they are by no means so well known as the acute manifestations of the disease. Among the types of disease and the by-products of this disease, fulminant, subacute and chronic types of hepatitis, cholangiolitic cirrhosis and artificially transmitted hepatitis will be discussed.

Fulminant Hepatitis.—This condition may be described as a fatal form of the disease which pursues its entire course within ten days. Clinically the condition corresponds to the often described acute yellow atrophy of the liver with which it is probably identical. Certainly there are no important clinical or pathologic differences. It is of some interest to note that epidemics in the past have been followed by a notable increase in the occurrence of cases of fulminating hepatitis. The most striking feature of this disease is the rapid development of severe hepatic insufficiency which often is attended by neurologic findings of great variety, rarely by hypoglycemic seizures and not infrequently by a hemorrhagic diathesis. At necropsy the principal findings are those which pertain to the liver; in this organ extensive and widespread necrosis of the lobules and complete

disorganization of the cell structure are evident. Lucké and Mallory have described the experience of the United States Army in the period between August, 1943, and April, 1945. There were 106 fatalities from epidemic hepatitis during this time, 53 per cent of which were of the fulminant variety. They noted that not a single case of fulminant hepatitis was reported during the 1942 epidemic of hepatitis which followed inoculation for yellow fever. In more than half of the fatal cases the fulminant hepatitis apparently was due to the transmission of an icterogenic agent contained in blood or serum.

A number of explanations for the sudden increase in these cases has been suggested. A difference in strains of virus may be considered or an increase in the virulence in the virus through repeated human passage. Host factors are probably important since many of the victims had been subjected to the rigors of combat and to other abnormal living conditions.

Subacute and Chronic Hepatitis without Jaundice.—Barker, Cripps and Allen called attention to this important group of cases. Eighteen per cent of a group of 431 unselected cases of epidemic hepatitis studied by them could be so classified on the basis of some evidence of hepatic disease more than four months after the first appearance of symptoms. In their patients little or no jaundice was seen as a late manifestation of epidemic hepatitis, the principal findings were hepatic enlargement and functional disturbances of liver of varying degrees as revealed by appropriate tests. The symptoms in these cases were not characteristic, in fact, many of the patients had been considered psychiatric casualties. These patients remained moderately ill and incapacitated for military service for months and often exacerbations of the disease developed on physical exercise or on return to full duty. These relapses often were manifested by increases in the size of the liver and deviations from the normal in the results of tests of liver function.

Neefe made some observations on a group of volunteers who had been inoculated with a strain of virus obtained in the course of an epidemic in a summer camp. In 10 per cent of this group clinical evidence of a chronic hepatitis developed and biopsy examination of specimens of the livers of two of them, obtained by the punch method, gave indisputable evidence of hepatic damage six and nine months after supposed recovery. The usual studies of hepatic function gave essentially normal results in these patients and in one other individual who gave a similar history.

It is certain that many individuals who have had infectious hepatitis still bear its anatomic and functional scars. Their possible status as carriers of virus and their future welfare are subjects of great theoretical and practical interest.

The Syndrome of Cholangiolitic Cirrhosis.—This syndrome was rescued from the catch-basket of biliary cirrhosis chiefly by the observations of Watson and Hoffbauer. They noted a type of hepatitis associated with chronic and rather constant jaundice and characterized by relatively normal hepatocellular function in the presence of the phenomena usually associated with regurgitation jaundice, such as increases in concentration of serum bilirubin, cholesterol and phosphatase and possibly bile salts, as shown by intense pruritus. The pathologic changes in many cases are minimal and are confined chiefly to the portal triads and finer bile ducts. The particular

point which concerns me at present is that in certain of these cases the illness began with what might well be regarded as infectious hepatitis and in one case described by Watson and Hoffbauer several biopsies over a period of nine years revealed gradual progression from mild hepatitis, possibly of epidemic origin, to advanced atrophic cirrhosis with periportal lymphocytic infiltration. It has been suggested that some chemical or viral stimulus may persist following hepatitis which causes proliferation of connective tissue and which could explain the gradually increasing strangulation of liver tissue by periportal infiltration. The relation of such types of cirrhosis to infectious jaundice must remain sub judice until better methods of identifying the virus become available.

It will be of interest to follow other cases of chronic biliary cirrhosis of the so-called Hanot type with the possibility of an infectious origin in mind. This seems particularly appropriate in view of the reported occurrence of a similar but much more progressive disease in Denmark. This is a strictly "word of mouth" report and concerns the development of a progressively fatal form of hepatitis with jaundice among women of post-menopausal age. In all these cases the condition appeared to be ordinary epidemic infectious hepatitis. However, the jaundice did not clear; evidence of hepatic functional damage increased and death occurred in a year or more with the usual signs and symptoms of chronic hepatic insufficiency. Full and detailed reports undoubtedly will be forthcoming in the near future. The age and sex factors are of an unusual nature although it has long been known that infectious hepatitis may be a more serious disease in older age groups.

Homologous Serum Jaundice.—By far the most clinically significant development in the field of hepatitis has to do with the appearance of homologous serum jaundice. This condition may be defined as that variety of hepatitis which develops following the parenteral introduction of a particular icterogenic agent (virus SH). It is characterized by a long incubation period (sixty to 120 days) and often by a fulminant and fatal course. The icterogenic agent causing it is remarkable for its resistance to all attempts to destroy it or render it inactive.

Serum hepatitis has been observed after the use of measles and mumps convalescent serum, whole blood, pooled plasma, both liquid and dried, and both yellow fever and pappataci fever vaccine contaminated with icterogenic serum. It has an appreciable mortality rate which is as high as 20 per cent in some series; this may reflect in part the condition of the patients (often injured or wounded men) rather than the natural virulence of different strains of the icterogenic agent. The size of the inoculum appears to make little or no difference, since serious hepatitis has followed the administration of 0.01 c.c. of the icterogenic agent while much larger doses appear to have produced a condition of about the ordinary degree of severity.

The appearance of homologous serum jaundice during a time when world-wide epidemics of infectious or epidemic hepatitis were raging suggests some connection between them, yet their incubation periods and some immunologic factors differ at least. Incidentally, the incubation period of the naturally occurring disease remains short even when the virus is given parenterally.

It seems clear that there is homologous but not heterologous immunity to the two forms of hepatitis. Volunteers inoculated parenterally with the serum transmitted disease (*serum hepatitis*) are not protected by a previous attack of the naturally occurring epidemic form, the converse of this proposition is also true. However, cases are on record in which blood from a donor in the preicteric phase of fulminant epidemic hepatitis induced a serious attack of serum hepatitis in the recipient after a rather long incubation period. The feces of individuals with serum hepatitis are not infectious to others whereas in the epidemic form the feces do contain the virus. There are some bits of rather doubtful evidence to show that the serum-borne form of hepatitis may be transferred to others via the intestinal tract, but these need further clarification. The serum from patients with homologous serum jaundice, as early as sixty days prior to the development of symptoms, may be highly infectious when given parenterally; the ietogenic agent also is present in the victim's serum during the height of the disease, but has not been demonstrated two months later. It is not present in stools. Such tests as the cephalin-cholesterol flocculation and brom-sulfalein often give positive results well before jaundice appears, and I have seen these tests give positive results at least a month before the appearance of fulminant and fatal serum-borne hepatitis.

The clinical importance of this method of transmitting disease can hardly be overestimated, especially since the use of whole blood, plasma and other biologic products for parenteral administration is now so well established. Bradley's figures from the Emergency Medical Service of Great Britain showed that the incidence of jaundice was 100 times higher in casualties who had undergone transfusion than in those not so treated. At one time homologous serum jaundice following the use of blood or plasma was the commonest cause of death in the United States army hospitals in England, accidents and pneumonia excepted. The experiences in one naval hospital have been cited by Wood, Meienberg and the writer. In a small series of cases of homologous serum jaundice the mortality rate was about 20 per cent. I have personal knowledge of another outbreak following the use of scarlet fever immune serum which also was attended with a distressingly high mortality rate.

The disease may be spread not only by blood and blood products but by contaminated syringes. The disease has been described in diabetic and ebrysotherapy clinics in which multiple injections were given from single syringes and a similar experience has been reported from several venereal disease clinics in which arsphenamine is given in this way. In at least one British clinic where "late arsphenamine jaundice" was a common development during the second or third month of treatment, the disease practically disappeared when individual syringes were substituted for the original multiple injection technic. So well established has this form of hepatitis become that I am inclined to agree with Bradley in the following statement: "When hepatitis occurs forty to one-hundred and twenty days after the administration of a human blood product or other parenteral therapy, it is almost certainly homologous serum jaundice and must be treated as a disease with an appreciable mortality." The reason for the long incubation period is as yet unknown; it does not depend on the route of inoculation alone.

Means of Prevention.—The means of prevention of homologous serum jaundice are of the greatest importance. Obviously donors of blood to be used either in the original state or as plasma should be questioned carefully for any history of illness. Many more data are needed in regard to the possible persistence of the virus in the serum in cases of supposedly healed epidemic disease. Nonjaundiced persons who had epidemic hepatitis, of whom there are believed to be many, may be carriers of the ieterogenic agent as well as individuals known to have been jaundiced. It has been suggested that some simple test, such as the thymol turbidity test previously mentioned, be made a part of the examination of each donor's blood. Suggestions also have been made as to the size of the pool of blood from which plasma is made. Large pools would tend to dilute the ieterogenic agent, but in view of the extremely small amounts required to transmit the disease, this method of prevention does not appear practical. Small pools of course would tend to reduce the mathematical chances of transmission. The present technic of collecting plasma is unsatisfactory as shown by a number of instances in which the pooled plasma of eight donors has produced homologous serum jaundice in 50 to 75 per cent of the recipients. Treatment of the plasma with ultraviolet light has been suggested by Oliphant and Hollaender. This method seems to be of some value. The plasma proteins may be altered somewhat, but there is no evidence of damage to antiviral and antibacterial substances.

Active prevention is still in the experimental stage. The importance of maintaining a diet high in protein and sources of vitamin B complex in patients receiving transfusions or plasma is obvious. The use of gamma globulin as a possible preventive measure is still under investigation. Some recorded observations seem to indicate that two doses of gamma (measles) globulin of 10 c c. each about a month apart furnish some degree of protection against homologous serum jaundice. Single doses may attenuate the epidemic form of the disease.

PORTAL CIRRHOSIS

The Liver and the Metabolism of Internal Secretions.—The biologic aspects of cirrhosis continue to attract the attention of investigators everywhere. Among recent contributions to this subject are some which pertain to endocrine disturbances. Earlier mention was made of a rapid and progressive form of cirrhosis affecting women past the menopause. The observations of the Biskinds on the role of the liver in inactivating estrogens are of interest in this connection, although they do not explain this peculiar type of cirrhosis. Biskind and Biskind showed, by placing pellets of either estrogenic or androgenic substances in the spleen of castrated rats, that the liver inactivated these substances more or less completely. Results with estrogens were far more conclusive than those with androgens. Transplanting the spleen so that the blood containing the implanted material did not pass through the liver, produced the specific estrogenic effect in castrated female rats. Hepatic damage and nutritional disturbances of a relatively small degree produced a similar effect; under such circumstances the liver apparently lost its power of inactivating the material.

The failure of the liver to inactivate estrogens explains certain physical findings in men who have cirrhosis which have not previously been appre-

ciated. Edmondson and his associates have shown that in men who have cirrhosis there may be an increased secretion of combined estrogens and considerable amounts of free estrogen in the urine. Estrogenic activity in men is often shown clinically by what has been called the "Silvestrini-Corda syndrome," a lack of bodily hair, an eunuchoid build, loss of libido, sterility, testicular atrophy and gynecomastia. Salter studied the last-mentioned phenomenon in malnourished prisoners of war. Without going into the details of his report, it seems clear that damage to the liver with corresponding failure to inactivate normally occurring estrogenic material is responsible for this change. In his patients gynecomastia disappeared as general nutrition, and presumably hepatic function, improved.

An even more interesting angle to this matter concerns the development of cutaneous arterial spiders (or *nevi araneosi*) and palmar erythema. The arterial spiders, so commonly seen in cirrhosis, have a histologic structure suggesting the spiral arteries of the endometrium. Bean has demonstrated that they may increase in size when estrogens are given to cirrhotic patients and new lesions (spiders) may form. These "spiders" may be seen in severe or prolonged infectious hepatitis, and may disappear as recovery takes place. Palmar erythema follows a parallel course. There is, in short, reason to regard both the spiders and erythema as by-products of estrogenic activity which would normally be suppressed by the liver.

Other hormonal substances which are inactivated by the liver normally are found in the animal organism. At least one such substance has been studied by Ralli and her collaborators. They found in a study of cirrhosis and ascites, as had other workers previously, that neither the serum albumin nor the osmotic pressure exerted by the serum was of such a magnitude as always to explain the transudation of fluid into the peritoneal cavity. For example, they noted in certain cases in which ascites had disappeared during treatment, that the osmotic pressure of the serum was about the same as it had been when ascites was present; hence, they assumed that some factors other than the concentration of albumin in serum were responsible. They, therefore, examined the antidiuretic effect of aliquots of dialyzed urine from these patients. The urine of patients with ascites when injected into hydrated rats markedly delayed the excretion of urine, while urine from patients with liver disease who had never shown ascites had an antidiuretic effect comparable to that found in normal urine. Patients who had previously had ascites but who were free from it at the time of examination excreted urine which had an antidiuretic effect midway between that of normal persons and that of patients with ascites.

The difficulty that the liver may have in inactivating this antidiuretic substance in acute disease is suggested by the recent observations of Labby and Hongland on water retention in acute infectious hepatitis. They noted a considerable degree of water retention in the acute phase of the disease. This retained water plus a considerable amount of chloride apparently was held entirely in the interstitial tissues as shown by simultaneous determinations of plasma volume and interstitial fluid volume (thiocyanate space). Water retention tests gave positive results during the acute disease when the concentration of plasma and urinary chlorides often was reduced. With convalescence there was often definite diuresis with restoration to normal of these various factors. It seems clear that changes of this magni-

tude could hardly be produced so rapidly by alterations of the plasma proteins, and these investigators suggested again that the inactivating properties of the liver might play a determining role.

Nutritional Aspects.—Cirrhosis of the liver now is regarded by many as a disease which may have a nutritional disturbance as its principal etiologic agent. Evidence on this point is to date largely circumstantial and derives from a large number of experiments on animals. Those of Glynn and Himsworth are representative; they produced necrosis of the liver of the rat by simple protein deprivation; the diet was adequate in all other respects. The addition of casein or of methionine alone to the previous diet was fully protective.

Some observations on prisoners of war tend to support the theory that extensive hepatic change in the human being may be produced by diet alone. In nineteen of a group of fifty such patients studied by Meienberg and me, hepatic enlargement, edema and disturbances in hepatic function as revealed by various tests were found singularly or in combination. While it seems apparent that few physicians will encounter cirrhosis dependent on a purely dietetic basis, yet these observations add strong support to the present conception of cirrhosis as a disease with a nutritional background, if only in the sense that dietetic factors render the liver vulnerable to hepatotoxic substances and virus infection.

Treatment.—The treatment of cirrhosis has undergone considerable revision since Patek's original plan of dietetic and vitamin therapy was advanced ten years ago. The fundamental principle of treatment by the maintenance of an optimal state of nutrition has not changed, however. Intake of protein has been increased, although this had formerly been interdicted on the basis of old experiments on dogs with Eck fistulas and of other studies which related the onset of ascites to the giving of meat digests. Intake of fat has been greatly liberalized. The intake of vitamins employed as treatment is essentially unchanged. Use of various specific medicaments, chiefly lipotropic substances, has been studied also. Choline and cystine may be valuable in treatment of alcoholic cirrhosis, but there is little evidence of their value in cases of nonalcoholic origin. Methionine given alone or in protein digests may have its place; some good results from its use have been claimed but its value is not proved. It is certain that it is of no value in epidemic hepatitis. Liver extract also is enjoying a therapeutic vogue. Some favorable results have been reported from use of crude preparations.

THE WHIPPLE OPERATION FOR CARCINOMA OF THE PANCREAS AND AMPULLA OF VATER

Formerly surgical procedures for carcinoma of the pancreas were limited to exploratory operation or cholecystogastrectomy or both. More radical measures were attended by a prohibitive mortality. As a result of Whipple's pioneer work, improved methods of anesthesia and means of controlling hemorrhagic states incidental to jaundice, a considerable number of surgeons have successfully removed portions or all of the pancreas and re-established continuity of the intestinal and biliary tracts by various means.

Waugh and Clagett recently reported the results of thirty such pro-

cedures with an over-all mortality of 20 per cent. An analysis of their figures brings out the fact that a single-stage procedure involving removal of the head of the pancreas could be done with about 8 per cent risk, while the two-stage procedure, which was used chiefly in the treatment of patients in poor general condition, or those on whom an exploratory operation had been performed previously, was considerably more hazardous. The duration of the jaundice in the two groups was not stated. However, it has been the general experience that the mortality rate following operations done for the relief of obstructive jaundice increases in direct proportion to the duration of jaundice. Hence if the patient who has pancreatic carcinoma is to receive the benefit of the greater safety of the one-stage operation, diagnosis must be made earlier before hydrohepatosis has damaged the liver too severely.

The question frequently asked is, Are there any means of establishing an early diagnosis? It is believed that there are, and that they should be more generally employed. The following points are worthy of mention in this connection: 1. Carcinoma of the pancreas almost always produces a complete mechanical obstruction whereas biliary stricture and stone rarely do. 2. Both of the latter conditions produce, as a rule, early and definite evidence of hepatic dysfunction whereas pancreatic carcinoma does so only after the lapse of considerable time. It is as a rule relatively easy by using tests of hepatic function, to exclude acute parenchymatous hepatic disease. To establish the presence of complete mechanical biliary obstruction is not so simple. Simple inspection of the stools and repeated Schmidt's tests for fecal urobilin are not too satisfactory. Duodenal intubation, formerly considered a reliable method of determining whether complete obstruction was present, is now under suspicion.

Stokes, who is studying the reliability of all methods for determining the existence of biliary obstruction, has permitted me to mention some of his preliminary studies. When no bile was obtained by duodenal drainage in his cases, the position of the tube was checked roentgenologically. In 78 per cent of such cases the tube was in the stomach rather than in the duodenum. Even when duodenal drainage did not produce bile, determinations of urobilinogen in the stools showed values above the range of those indicative of complete obstruction in 53 per cent of his cases. In five cases in which no bile was obtained on drainage of the duodenum and roentgenologic examination had demonstrated that the tube was in the duodenum, the concentration of urobilinogen in the stool was above the range of that for malignant obstruction and, in fact was within the normal range in four of the five cases. In no case was bile found in the duodenal content when the concentration of urobilinogen in the stool was in the range of complete obstruction.

These observations indicate clearly that the only physiologically satisfactory proof of complete biliary obstruction (which is, of course, the rule in occlusion of the biliary passages by malignant lesions) lies in the demonstration of low levels of fecal and urinary urobilinogen. Although these determinations are tedious, they seem definitely in order when a procedure of such magnitude as the Whipple operation for pancreatic carcinoma is under consideration.

The postoperative care of these patients is now receiving particular study

and some patients who have undergone the Whipple operation have been observed in a metabolic unit and the findings have been compared to those for patients who have undergone gastric resection. Details are not yet complete but certain points may be mentioned. 1. The gastric resection associated with the Whipple operation contributes definitely to losses of fat and nitrogen in the feces. 2. Partial pancreatectomy is followed by considerable creatorrhea and steatorrhea; patients are likely to remain in negative nitrogen balance during the postoperative state. Pancreatin in adequate dosage reduces losses of fat and nitrogen by about 50 per cent. 3. Diabetes in one case was not increased in severity by partial pancreatectomy. 4. Fatty livers observed in pancreatectomized dogs do not develop in patients. 5. Nutritional disturbances observed in the late postoperative period are less than anticipated in spite of the findings just listed.

It is likely that further reports on the late mortality of these patients will be forthcoming, as well as additional observations on the metabolic effects of and the morbidity from the procedure itself. Until these are completed, the value of the operation cannot be determined finally.

ADVANCES IN THE TREATMENT OF CHRONIC HEPATIC DISEASE*

ALBERT M. SNELL

Prior to the year 1930, treatment of hepatic cirrhosis was largely a matter of attempting to rid the body of extraneous collections of fluid and to reduce jaundice by various means. Purgation, restricted diets, diuretics of various types, mercury and iodides and other radical remedies were extensively used. It is not remarkable that few patients survived their first paracentesis. With the revival of interest in hepatic physiology which developed following the first reports on experimental hepatectomy, some improvement in the program of treatment was noted and the first serious attempts were made to supply a high caloric, high carbohydrate diet to the patient. Injectable mercurial diuretics were a distinct asset in therapy; their use was rarely attended with serious consequences and, as a result, time of survival of these patients was somewhat prolonged. The first publication on the methods of treatment now in general use was that of Patek in 1937. Out of his observations a whole new scheme of treatment has developed.

Treatment of cirrhosis today is predicated on several well-defined ideas: (1) Chronic hepatic disease is, in many instances, of nutritional origin; the nutritional defect may be the sole cause of the disease or it may have contributed to a reduced resistance of the liver in respect to toxins, viruses and the like. (2) The significant nutritional defect probably lies in both quality and quantity of protein in the diet and in the intake of the vitamin B complex. (3) Some of the most characteristic features of the disease have to do with defective protein metabolism and with qualitative and quantitative changes in the plasma proteins. (4) As the disease advances, addi-

* From the Chicago Medical Society Bulletin, 50 153-156 (Aug. 23) 1917.

tional disorders of nutrition involving various vitamin deficiencies develop. (5) The process of hepatic disintegration and the resulting deficiency states are reversible in a substantial percentage of cases.

To review the experimental and clinical evidence on which these ideas are based would greatly exceed the scope of this report. Recent publications by Morrison, Hoagland and others should be consulted by those interested. It suffices to say that a dietary intake low in protein and in the vitamin B complex has been observed to be responsible for the production of cirrhosis in human beings and animals. In Syria, China, South Africa and India deficient diets are clearly responsible for the high observed incidence of cirrhosis; the condition has also been encountered among semistarved prisoners of war. Alcohol, which has been believed to account for about 30 per cent of the cases of cirrhosis encountered in American clinics, does not complicate the picture in such cases. In other words, cirrhosis may develop on purely nutritional grounds, the combination of alcohol and an inadequate diet merely accelerates the process.

In attempting to narrow the field of missing dietary constituents responsible for cirrhosis, a few specific protective substances have been demonstrated, notably choline, which is a known lipotropic agent, methionine, betaine and cystine. For details of the manner in which these substances are involved in the pathogenesis of cirrhosis, the reader is referred to Gyorgy's recent excellent review. These last-mentioned agents are of course all present in satisfactory concentration in an optimal diet. Information in regard to the specific action of vitamins in protecting against hepatic injury is not nearly so complete. It is believed, however, that natural sources of the B complex, notably yeast and liver, contain some specific substances of protective value other than methionine and choline. The fraction (or fractions) responsible are not as yet known.

DIET IN CIRRHOSIS

The original diet advocated by Patek, which has been extensively modified and used by other workers, contained 365 gm. of carbohydrate, 129 gm. of protein and 175 gm. of fat. The diet originally in use at the Mayo Clinic, as reported by Fleming and inc, contained 500 gm. of carbohydrate, 110 gm. of protein and 60 gm. of fat. The diet used by Hoagland and his associates resembled closely that of Patek. It has been demonstrated that a high fat diet is not only well tolerated in epidemic hepatitis but that recovery of weight and strength is more rapid when such a diet is employed. *Subsequent experience with the Mayo Clinic diet* has also led to a more liberal use of fat, which increases the palatability of the diet and makes it more adaptable for use in the patient's home. There are some theoretical reasons for using fats high in unsaturated fatty acids. Most clinicians find it necessary to make this diet fairly concentrated and to derive most of the protein and fat from milk, eggs, cream, cottage cheese and baked or boiled meats. The milk may be fortified with powdered milk, powdered egg and special preparations of high protein content, such as dietene. For patients unable to take solid food, special feeding formulas suitable for introduction by duodenal tube have been employed. It now appears that the exact composition of the diet is of no great importance provided it contains 300 gm. or more of carbohydrate and 150 gm. or more of protein and pro-

vides a total intake of 2,500 to 4,000 calories. It should be palatable and attractive, since many patients who have cirrhosis have little taste for food.

The extent to which this diet should be supplemented with vitamins is as yet undecided. Morrison advised one high potency multivitamin capsule daily, plus two capsules of a B complex preparation three times daily. Patek used thiamine and brewers' yeast as supplements. It is our present practice to give 15 to 30 gm. of brewers' yeast three times daily in tomato juice, plus two or three multivitamin capsules daily. The diet and the vitamin concentrations form what may be called the basic ration. Other vitamin concentrates may be used as indicated and since there is often good clinical evidence of deficiency in respect to vitamins A, D and K, it is customary to include them in any dietetic program.

All of the foregoing programs have been supplemented by the parenteral injection of liver extract in various doses two to three times a week. The basis for liver therapy is not entirely well founded scientifically and yet it seems to be of distinct value. It appears to stem from the French school of organotherapy (about 1900) and has been reviewed at intervals for some years. The most recent stimulus has been provided by the Rockefeller Institute group, who have used large doses of a special preparation of liver extract (intraheptol) intravenously. After a careful preliminary check of the patient for sensitivity, increasing doses may be administered until a total of 10 c.c. is given daily, diluted to 50 c.c. with isotonic saline or glucose solution. The usual clinical effect is an increase of appetite and of the patient's sense of well-being. Morrison's report and one which will appear shortly from the Rockefeller Institute seem to indicate clearly the clinical usefulness of the procedure and the favorable effect on the course of the disease. The disappearance of ascites is often noted and the period of survival is lengthened. The experience of my colleagues and myself with intravenous administration of liver extract has been somewhat disturbed by untoward reactions but some encouraging results are already apparent and its extended use is contemplated.

The preceding paragraphs give the basis of the dietetic program and outline the extent to which it is usually supplemented. There are many who feel that such specific protective substances as methionine, choline or choline plus cystine should also be added and one must admit that there is some theoretical possibility of improving the program in this way. György has recommended the use of 2 gm. of methionine daily, as did also Morrison. Methionine is an expensive preparation and not readily available; moreover, it is present in good concentration in a high protein diet. The use of methionine does not, incidentally, alter the course of epidemic hepatitis in any way. Choline is less difficult to obtain and administer than methionine and should almost certainly be used as a supplement, especially if the patient has an alcoholic background and a large and presumably fatty liver. The lecithin in the egg yolks contained in the diet again will probably supply all the choline that is needed under ordinary circumstances. Yet it must be admitted that the addition of choline, or choline plus cystine, in adequate quantities has produced some over-all improvement in clinical results (Beams, Morrison). No well-controlled data are available to give a definite answer to the question and it appears that it may be well to continue to use these specific agents pending further developments in the field.

vitallium tubes and avoiding the use of sutures. In a series of cases reported by them, recurring hemorrhages from esophageal vessels have been controlled, ascites has disappeared in some cases and even improvement of hepatic function has been reported. Their reports should be carefully studied, since the work represents a major advance in a most difficult field.

Success in treatment of cirrhosis depends on many factors, earlier diagnosis, attention to detail and a diversification of the known adjuvants in therapy, as well as patience and persistence. Any agent which will increase the total metabolic efficiency of the damaged liver or correct any part of the deficiency state produced by it should be employed. Since most patients who have clinically demonstrable chronic hepatic disease are far advanced in the process of hepatic destruction when first seen, it is not likely that the patient will be overtreated. The alcoholic patient, who cannot afford a single lapse from abstinence, may need expert psychiatric guidance. Minor infectious processes and trauma require special care, since they may be followed by a period of rapid decline. The most important single consideration is the maintenance of a normal calorie, protein and vitamin intake by whatever means may be feasible.

RESULTS OF TREATMENT

The results of treatment are considerably beyond expectation considering the age group involved and the advanced state of hepatic injury at the time treatment was begun. Fleming and I reported in 1942 on fifty patients treated by the methods outlined in this paper. Twenty patients were living after two years, of whom eleven were free from ascites; five others required only occasional tapping. Patek's most recently reported figures are even better, especially when considered in the light of his control series. Sixty-five per cent of his patients survived the first year as compared with 40 per cent of the controls; 50 per cent lived beyond the second year as compared with 20 per cent of the controls, and 30 per cent survived five years as against only 7 per cent of the controls. He described, as we have done also, repeated responses to treatment in the same patient, a most significant phenomenon. Morrison's figures are equally impressive; in a group of nine "compensated" cases of cirrhosis, all patients were living after a two year period; of eleven patients who had ascites, all but two survived over a two year period. There was a corresponding decrease in the period of disability as compared with a control group.

One may venture an optimistic guess in conclusion. With improved dietetic and vitamin therapy, a readily available supply of human serum albumin and the recent astonishing successes in the field of porta-caval anastomosis, portal cirrhosis may eventually be classified as a disease with a relatively good prognosis for continued life and health.

hepatitis in which anorexia interferes with a normal dietary intake and a positive nitrogen balance cannot therefore be attained. These encouraging reports should stimulate a further clinical use of albumin when it becomes more generally available.

Hepatic Coma.—This condition, the common terminal manifestation of advanced hepatic insufficiency, is more often than not beyond the reach of treatment. In an occasional case, the patient may respond. I have personally observed a number of recoveries, and good results in the precomatose state are fairly common. Coma is often precipitated by a hemorrhage, tapping, a standard dose of barbiturates or an intercurrent infection and may develop with great rapidity. There are two important factors to bear in mind—these patients have anoxia, and many show the neurologic features of the encephalopathy encountered in such deficiency diseases as pellagra. Treatment should include transfusion of whole blood (to provide new and normal hemoglobin), an oxygen tent and the continuous infusion of solution of glucose containing at least 100 mg. of thiamine and 250 mg. of niacin daily. At least 1 liter a day of casein hydrolysates will assist in maintaining nitrogen metabolism. The use of cytochrome C has been considered because of its known effects on cerebral anoxia.

Hemorrhagic States.—These are most often due to prothrombin deficiency, which in turn is an expression of severe hepatic damage. Transfusion of blood should be relied on, unless the prothrombin time shows a positive response to the administration of vitamin K, which is only rarely the case. In occasional cases in which there is associated thrombopenia, the condition is virtually hopeless. Curiously enough, patients may be tided over successive crises of prothrombin deficiency and make a satisfactory recovery.

Hemorrhage from Esophageal Varices.—This is a fairly common occurrence, especially in cirrhosis of long duration in which portal hypertension of intrahepatic origin is well advanced. The patient may become exsanguinated with the first hemorrhage or he may survive many hemorrhages of lesser magnitude over a period of years. No entirely satisfactory method of treatment is currently available. Splenectomy, omentopexy and ligation of the coronary veins of the stomach, used singly or in combination, have all produced some satisfactory results and have also been attended by many failures. A direct attack on the esophageal vessels through the esophagoscope with the use of a sclerosing solution may be successful if the varicose vessels do not extend into the cardiac end of the stomach. The procedure is difficult, tedious and dangerous except in the hands of expert endoscopists.

The recent studies of Whipple and of his associates, Blakemore and Lord, offer the greatest encouragement to those seeking relief from portal hypertension and recurring hemorrhages. They have demonstrated portal pressures as high as 400 to 500 mm. of water (four to five times the normal) in patients who had Banti's syndrome and portal cirrhosis. Because of this heightened venous pressure it is possible to make an anastomosis to another adjacent vein with a lower hydrostatic pressure with good prospects of permanence. Two procedures have been tried: (1) anastomosis between the severed splenic vein and the left renal vein, the spleen and left kidney being simultaneously removed; (2) portacaval anastomosis in the manner of an Eck fistula. The good results of Whipple and of Blakemore and Lord depend on a newly developed technique for anastomosis of blood vessels, using

vitalium tubes and avoiding the use of sutures. In a series of cases reported by them, recurring hemorrhages from esophageal vessels have been controlled, ascites has disappeared in some cases and even improvement of hepatic function has been reported. Their reports should be carefully studied, since the work represents a major advance in a most difficult field.

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One may venture an optimistic guess in conclusion. With improved dietetic and vitamin therapy, a readily available supply of human serum albumin and the recent astonishing successes in the field of portacaval anastomosis, portal cirrhosis may eventually be classified as a disease with a relatively good prognosis for continued life and health.

CHOLECYSTITIS; A STUDY OF INTRAMURAL DEPOSITS OF LIPIDS IN TWENTY-THREE SELECTED CASES*

RODGER E. WEISMANN AND JOHN R. McDONALD

A study of the clinical records and a gross and microscopic investigation of the specimens of gallbladder, combined with chemical determination of the lipid fraction present in the tissues, were carried out in twenty-three cases of advanced inflammatory disease of the gallbladder. Complete clinical and pathologic data are presented in all cases in the complete paper, while results of the determination of tissue lipid fractions are recorded in five of the twenty-three specimens. For control data, chemical studies were made of tissue from the wall of seven additional fresh gallbladder specimens.

The presence of advanced, complicated, inflammatory lesions of the gallbladder in the twenty-three selected cases was not associated with corresponding clinical evidence, preoperatively, of a severe infection or purulent intra-abdominal disorder. Furthermore, except in the one post-operative death, infection or sepsis did not complicate the recovery from the surgical procedures performed in the treatment of the disease.

The local lipid disturbances in the walls of the gallbladders were associated with active perforating purulent lesions but there was no clinical evidence of significant bacterial activity such as is usually seen in similar lesions which involve other intra-abdominal viscera such as the appendix. Obstruction of the cystic duct with resultant stasis or imprisonment of bile occurred in most, if not all, of these gallbladders.

In addition to many of the usual histopathologic changes seen in inflammation of the gallbladder, the twenty-three specimens revealed evidence of excessive deposits of lipids in either an intramural or pericholecystic location. For the most part, the lipids were in the form of intracellular deposits in large mononuclear phagocytes or giant cells. The lipids were associated with three types of histopathologic picture, namely, a xanthomatous granulomatous reaction, fat necrosis and intramural areas of dense cellular infiltration with necrosis and "abscess" formation. The histopathologic evidence presented, suggestive of a chemical origin of the cholecystitis seen in these patients, would explain the paucity or absence of clinical signs of infection or sepsis.

Chemical determinations of lipid fractions of the tissue from five of the gallbladders indicated that the cholesterol and cholesterol esters were significantly increased in those specimens which showed histopathologic evidence of excessive deposits of fatty substances. When fat necrosis predominated, there was a marked increase in the fatty acid fraction. When the other characteristic lipid lesions were seen, the fatty acid fraction was only slightly increased.

Rokitansky-Aschoff sinuses or diverticula of the gallbladder appeared to play an important role in the production of this type of inflammatory reaction. These frequently occurring structures in the wall of the gallbladder may explain these and other unusual features of cholecystic disease.

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The phenomena observed would suggest that chemical irritants or metabolic disturbances play a major role in the development of many of the inflammatory processes of the gallbladder

THE SILENT GALLSTONE: A TEN TO TWENTY YEAR FOLLOW-UP STUDY OF 112 CASES*

MANDRED W. COMFORT, HOWARD K. GRAY AND JAMES M. WILSON

In the hope of supplying some of the data not now available but necessary for decision regarding treatment of the silent gallstone, a long-term follow-up study of all cases in which gallstones were found incidentally during the course of some other abdominal operation at the Mayo Clinic was carried out. The records of 998 such cases occurring from 1925 through 1934 were reviewed. Approximately a half of these were discarded as unsuitable for long-term follow-up because the operation had been for cancer. Many others, including those with duodenal ulcer, were discarded because some of the abdominal symptoms might have been due to the cholelithiasis. Follow-up letters were sent to 184 persons. Replies were received from 115 (62 per cent). Each patient was asked if indigestion or colic had preceded the discovery of the gallstones and several replied that symptoms had been present, so that these, too, were discarded. Finally, 112 cases were considered suitable for study. The average age of the 112 patients was 48.2 years when the gallstones were discovered.

RESULTS OF STUDY

In thirty cases indigestion developed and it is assumed that the indigestion in each case was due to the disease of the gallbladder. Under the term "indigestion" are included those cases in which such symptoms as gaseous indigestion, intolerance to certain foods, and heartburn developed, as the only abdominal distress. The severity of the indigestion varied; some patients were bothered occasionally, a few were able to control all symptoms by diet while others felt that the indigestion was incapacitating.

Twenty-one patients reported colic; more than half had experienced more than one attack of colic, but several who had had frequent and severe attacks of colic found that sooner or later the attacks had subsided so that they had had no symptoms whatsoever for years. Five of the twenty-one patients had both colic and jaundice; of the five, four had had slight jaundice which followed an attack of colic and was transient only. The fifth patient underwent operation immediately after the first attack of colic and jaundice.

In a total of fifty-one (45.5 per cent) of the 112 cases symptoms developed. In twenty-four of these fifty-one cases cholecystectomy was performed. Three of the twenty-four patients died postoperatively. The death of the patient who underwent operation at the clinic was due to pulmonary

* *Abridgment of paper accepted by the Annals of Surgery*

embolism. Of the two who underwent operation elsewhere, one death was reported by the patient's relatives to be due to subphrenic abscess and the other to a "weeping" liver. In sixty-one (54.5 per cent) of the 112 cases abdominal symptoms did not develop before death or have not developed since the discovery of the gallstones.

It is of interest that twenty-eight of the patients have died. Of the twenty-eight, twenty-one did not, so far as can be ascertained, experience symptoms prior to death but seven did. The cause of death was unknown in four cases, while death was due to cancer in six, to heart disease in five, to infectious disease in five, to cerebral accident in four, to amputation of the leg in one, and followed cholecystectomy in three. In not one of the six cases in which the patient died of cancer was the gallbladder the seat of the cancer.

COMMENT

Although we recognize the limitations of the information obtained by follow-up letters, none the less, this study furnished interesting and thought-provoking data. Although these data do not give conclusive information about the risk of non-operative and operative treatment of the silent gallstone, they are noteworthy on this basis: that the patient with silent gallstone may be told that he has about an even chance that symptoms will develop, that he has about one chance out of five that painful seizures will develop and a small chance that jaundice will develop within ten to twenty years. In addition, he should be told that the risk of surgical intervention at the best is about 0.5 per cent when cholecystectomy is performed before complications develop, that the risk will increase to about 3 per cent if he defers surgical intervention until complications develop, or old age and physical debilities appear, but that the increase in risk is counterbalanced by the fact that if he defers surgical intervention he may never require operation. It is not possible on the basis of information now available to tell the patient whether the risk is greater or smaller if operation is performed while the gallstones are silent than if it is postponed until symptoms develop. Certainly, the mortality rate will be low regardless of the choice made.

The reaction of the patient to his problem will be an important determining factor. Many patients will prefer to have gallstones removed in order to eliminate the threat of painful seizures or severe complications. Others, knowing the higher risk of surgical intervention should complications develop, will prefer to take the chance that no symptoms will develop. Surgical treatment of the silent gallstone may be classified as optional or elective surgery, but surgical intervention should not be postponed after symptoms, and more especially after attacks of colic, appear.

LYMPH FROM LIVER AND THORACIC DUCT. AN EXPERIMENTAL STUDY*

JAMES C. CAIN, JOHN H. GRINDLAY, JESSE L. BOLLMAN, EUNICE V. FLOCK
AND FRANK C. MANN

The average rate of flow of hepatic lymph was 2.26 c.c. per ten minutes as compared with 4.6 c.c. per ten minutes for that of lymph in the thoracic duct. Probably hepatic lymph contributed a fourth to a half the total volume of lymph in the thoracic duct.

Intravenous administration of 20 per cent solution of glucose as a lymphagogue was followed by an increase of approximately 70 per cent in the rate of flow of lymph from both the liver and the thoracic duct.

Ingestion of food and brief periods of exercise were followed, in each instance, by an increase in the rate of flow of lymph from the thoracic duct and the liver. Ingestion of food increased the rate of flow of lymph from the thoracic ducts by approximately 80 per cent and that of hepatic lymph by approximately 105 per cent. Exercise increased the rate of flow in the thoracic duct much more precipitously than that from the hepatic fistula, probably because of the massaging effect of exercise on the large lymphatic beds.

Acute poisoning with carbon tetrachloride caused no gross change in the flow of lymph, but hepatic lymph became bloody. In the presence of cirrhosis caused by exposure to carbon tetrachloride the rate of flow of hepatic lymph was greatly increased but that of lymph from the thoracic duct was only moderately increased.

The protein content of hepatic lymph was approximately five sixths that of blood plasma and that of lymph from the thoracic duct was approximately half that of blood plasma. Lymph from both the liver and thoracic duct contained sugar and chloride slightly in excess of that found in blood plasma, the content of inorganic phosphate was the same in all three and the value for alkaline phosphatase was 30 to 50 per cent lower in lymph from each source than in blood plasma

RADICAL RESECTION OF HEAD OF PANCREAS AND TOTAL PANCREATECTOMY†

JOHN M. WAUGH

In the following review are included all cases in which radical resection of the head of the pancreas and the duodenum was attempted at the Mayo Clinic up to January 1, 1947. In all, forty-nine patients underwent a modi-

* Abstract of paper published in full in *Surgery, Gynecology and Obstetrics* 85:559-562 (Nov.) 1947.

† Abridgment of paper published in full in the *Journal of the American Medical Association* 137:141-144 (May 8) 1948

fied Whipple operation. There were thirteen deaths in the hospital, or an operative mortality rate of 26 per cent. Six patients underwent total pancreatectomy; one died. Forty-three underwent radical resection of the head of the pancreas and the duodenum; twelve of them died in the hospital, an operative mortality rate of 28 per cent.

A likely explanation for the lower mortality rate which accompanies total pancreatectomy is that (1) removal of the body and tail of the pancreas and the spleen adds little to the procedure of removal of the head of the pancreas and the duodenum, and (2) because the entire pancreas is excised, any leakage or fistula from the pancreatic stump is obviated. This does not indicate, however, that total pancreatectomy should be performed in preference to partial pancreatectomy when the latter will eradicate the disease, since the metabolic derangements which will follow total excision may outweigh any possible advantages of the more radical operation.

Although only eleven patients have been operated on for benign disease of the pancreas, it is interesting to note that the operative mortality rate for such an operation is more than twice that of pancreatectomy done for malignant disease. This is probably due to the greater technical difficulties that may arise when the surgeon is confronted with an inflammatory process that frequently becomes adherent to the superior mesenteric vein and may result in gross operative hemorrhage, such as happened in two instances among the eight persons operated on for chronic pancreatitis. The other two deaths resulted from peritonitis and massive pulmonary embolism, respectively. The fact that there were no deaths in the hospital after total pancreatectomy for chronic pancreatitis would bear out the point that it is exceedingly important to defer resection of a part or all of the pancreas for inflammatory conditions until the process is in the chronic end stage of calcification—as it was in all the successful resections—and not to attempt pancreatectomy in the face of subacute inflammation.

Naturally, all conservative measures, such as prolonged drainage of the common bile duct either by insertion of a T-tube or by choledochoduodenostomy, should be tried before resection is attempted. If these measures fail and the process of calcification is limited to the head of the pancreas and the pain is intractable, resection of the head of the pancreas should be undertaken. If, however, the calcification involves the entire pancreas, the pain remains intractable and there are associated diabetes and insufficiency of the external secretion, then total pancreatectomy is advisable. Already there are encouraging reports of relief obtained for patients with this type of pancreatitis by performance of thoracicolumbar sympathectomy alone or this type of operation associated with vagotomy. It is hoped that the late results will be satisfactory, since such procedures can be done with only a fraction of the risk of pancreatectomy.

Occasionally, total pancreatectomy will be necessary for islet-cell tumor. Total pancreatectomy has been performed three times at the Mayo Clinic among a total of forty-six patients in whom islet-cell tumors were found at surgical exploration during the past twenty years.

Before a patient undergoes total pancreatectomy for islet-cell tumor of the head of the pancreas, it is imperative to determine (1) that the patient's symptoms are due to spontaneous hypoglycemia, (2) that the tumor is not situated in the tail or body of the pancreas, where about 80 per cent of such

tumors are found, or in an accessory pancreas, (3) that if the tumor is situated in the head, local excision with preservation of the pancreas is not possible or that resection of the head of the pancreas, which would obviate diabetes and deficiency of external pancreatic secretion, is not possible and (4) that the symptoms and disability produced by the tumor outweigh the magnitude of the operation and the disturbance in metabolism which follows it.

If, after careful surgical exploration, a tumor is not palpable, it is usually advisable for the surgeon to resect the tail and body of the organ and, if on immediate careful examination of this specimen by the pathologist no tumor is found, the surgeon ought then to proceed with removal of the head of the pancreas.

A total of thirty-eight patients underwent operation for malignant processes. For thirty-seven of these radical resection of the head of the pancreas and the duodenum was performed and for one patient total pancreatectomy was done. There were eight deaths in the hospital, an operative mortality rate of 21 per cent. Among those patients who had malignant lesions, nineteen had carcinoma of the head of the pancreas, sixteen had carcinoma of the ampula or papilla, two had carcinoma of the duodenum, and one had extension of the malignant process into the head of the pancreas from a primary carcinoma of the stomach. It is pertinent and significant that fifteen patients underwent operation in one stage for carcinoma of the head of the pancreas, with an operative mortality rate of 13 per cent. This figure is very near that for palliative operations at the present time. The operative mortality rate for lesions of the ampulla of Vater was 23 per cent in the case of thirteen patients who underwent a one-stage operation. This is appreciably higher than the operative mortality rate among those who had carcinoma of the head of the pancreas. Actually, there should not be this difference in risk, and as the series becomes larger the discrepancy between the operative risk of lesions of the ampulla and that of lesions of the head of the pancreas will become less.

For the purpose of evaluation of survival beyond the immediate post-operative period, the group of thirty patients who had had a malignant lesion as reported by Clagett and me, and all operated on prior to January 1, 1940, were examined or reached by letter by February 1, 1947.

A total of twenty-four patients survived operation; fifteen had died in the interim from recurrence, and nine were living without definite evidence of carcinoma at the time the inquiry was made. The survival rate among those patients who had had carcinoma of the head of the pancreas is discouraging, for eleven of the fourteen surviving the operation already had succumbed at the time of inquiry. The average length of palliation for this group was 8.4 months. It is doubtful that palliation of greater duration was obtained from radical resection than might have been expected from cholecystogastrostomy or cholecystojejunostomy. The three patients still alive at the time of this inquiry had lived, on the average, eighteen months, and two of them had had involvement of lymph nodes. This is heartening, for at present radical resection offers the only hope of cure for these unfortunate patients, and because of the location of the pancreas the most radical type of resection possible is at most, so far as the node-bearing area is concerned, local excision.

The survival rate of patients after resection for carcinoma of the ampulla of Vater is, as might be expected, immeasurably better than that after resection for carcinoma of the head of the pancreas. Of eight surviving operation for the former lesion, three succumbed because of recurrence and five had been alive for an average of twenty-eight months at the time of this report. One of these was alive and well three years after operation. Those who obtained only palliation survived an average of thirteen months. It would appear that some of the patients who had carcinoma of the ampulla will secure permanent cure.

Although the results thus far recorded for the group with carcinoma of the head of the pancreas are discouraging, there is no other procedure which offers any hope of cure; hence, I feel that radical resection is justifiable and indicated for carcinoma arising in the ampulla of Vater or head of the pancreas. Furthermore, at the time of operation the surgeon may not be able to determine whether the lesion arises in the ampulla of Vater, head of the pancreas or duodenum. Even after resection, the pathologist may have difficulty in establishing the origin of the lesion.

It is obvious, then, that to give every patient his rightful opportunity for cure rather than only palliation, the surgeon will of necessity resect every lesion possible, hoping that it will prove to be a lesion of the ampulla of Vater. Naturally, the earlier in the course of the disease these patients are operated on, the better the chance of cure will be.

Jaundice should be considered an indication for surgical exploration unless incontrovertible evidence is at hand to justify medical management. The fact that the jaundice disappears spontaneously or is intermittent or mild is no sign that it is of benign origin. Several patients in our series had intermittent jaundice in the presence of carcinoma of the ampulla of Vater, and in one instance recently jaundice had entirely resolved after its first appearance.

The Whipple procedure, or a modification of it, also provides a curative operation for primary carcinoma of the duodenum. One patient who survived this operation in the present series was alive, well and active twenty-two months postoperatively.

So far as the mortality rate is concerned, the one-stage operation in our experience has produced a lower figure. Most patients will present themselves in reasonably good condition, so that with the accepted preoperative preparation the single-stage operation certainly will be associated with no increased hazard. The one-stage procedure has the advantages of eradication of the malignant process at an earlier date, so that the patient is spared the discomfort and expense of two major operative procedures. The operation also usually permits easier and more rapidly executed resection. Certain patients, however, are in such poor condition when they come for treatment that performance of a two-stage procedure is obligatory. By careful preoperative analysis the condition of such patients, as a rule can be determined with little difficulty.

In an analysis of the first thirty cases of radical resection of the head of the pancreas and duodenum at the Mayo Clinic, various methods of drainage of the biliary and pancreatic ducts and restoration of gastro-intestinal continuity were compared. Conclusions were reached which it has not been necessary to change with further experience. Performance of end-to-end

pancreaticojejunostomy, end-to-side choledochojejunostomy and end-to-side, postcolic, antiperistaltic gastrojejunostomy has proved to be satisfactory and seems physiologically and anatomically sound (fig. 19). This

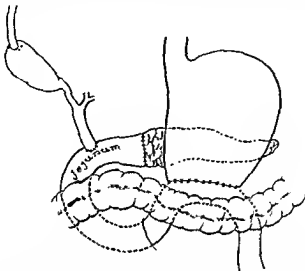


Fig 19 —Technic for restoration of continuity of the gastro-intestinal tract, biliary and pancreatic ducts after resection of the duodenum and head of pancreas (end-to-end pancreatico-jejunostomy, end-to-side choledochojejunostomy, end-to-side, postcolic, antiperistaltic gastrojejunostomy) (From Waugh, J M. Resection of the head of the pancreas and duodenum operative technic S Clin North America 26:215 [Aug] 1946.)

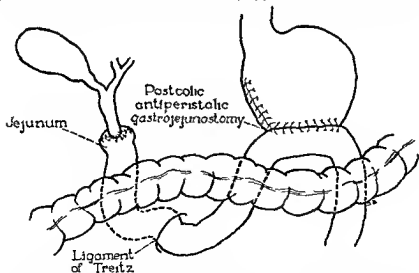


Fig 20 —Technic for restoration of continuity of the gastro-intestinal tract and biliary ducts after total pancreatectomy (end-to-end choledochojejunostomy, end-to-side, postcolic, antiperistaltic gastrojejunostomy).

technic more or less isolates the biliary and pancreatic systems, so that food and the gastric secretions are shunted distally. This isolation may prevent cholangitis. Furthermore, if a malignant lesion should recur, it would not

be likely to obstruct the gastro-enteric stoma. The technic of total pancreatectomy, as far as revision of the gastro-intestinal tract is concerned, is the same, but end-to-end choledochojejunostomy is utilized since no pancreatic stump remains which requires drainage into the jejunum (fig. 20).

SUMMARY

Radical resection of the head of the pancreas and of the duodenum had been done forty-nine times at the Mayo Clinic up to January 1, 1947. Eleven operations were for benign disease and thirty-eight for malignant lesions. Six patients underwent total pancreatectomy, with one death in the hospital. The indications for resection of the head of the pancreas and total pancreatectomy for benign disease are discussed and it is emphasized that in such instances resection should be carried out only after careful evaluation of both the operative risk entailed and the disturbances in metabolism which might be expected. Resection for carcinoma was accompanied by an operative mortality rate of 21 per cent. In the future this figure should become lower, for already one-stage resection for carcinoma of the head of the pancreas has been performed fifteen times with a hospital mortality rate of only 13 per cent.

A follow-up study of the thirty patients who had undergone resection for malignant processes prior to January 1, 1946, and had survived operation, showed that three of fourteen who had had carcinoma of the head of the pancreas and five of eight who had had carcinoma of the ampulla of Vater were still alive on that date. When it is considered that, other than surgical treatment, there is no therapeutic measure available which gives these patients any chance for cure, we should constantly strive to lower the operative mortality rate for the procedure and improve diagnostic acumen, so that resection can be carried out more often while the carcinoma is still in a curative stage.

THE PANCREAS IN UREMIA: A HISTOPATHOLOGIC STUDY*

ARCHIE H. BAGGENSTOSS

Histologic examination of the pancreas at necropsy in subjects in which death had resulted from uremia frequently revealed a remarkable degree of dilatation of the acini, flattening of the lining epithelial cells and inspissation of secretion. The lesion was found in thirty-three (39 per cent) of the eighty-five cases of uremia resulting from chronic glomerulonephritis, in thirty-six (42 per cent) of the eighty-five cases of uremia resulting from hypertension (nephrosclerosis) and in fifty-two (52 per cent) of the one hundred cases of uremia resulting from miscellaneous causes. Neither age, sex, degree nor duration of azotemia appeared to play a significant role in the production of the lesion. In the control series of 200 cases in which uremia did not occur the lesion was present in mild or moderate degree in

* Abstract of paper published in full in the *American Journal of Pathology*. (In press)

forty cases (20 per cent). The most common cause of death in the control series was intestinal obstruction. It is suggested that dehydration plus an interference with the release and normal action of secretin brought about by excessive vomiting are responsible for the lesion. It is also suggested that either a congenital lack of secretin or some defect in the mechanism of its release may be responsible for so-called fibrocystic disease of the pancreas.

PANCREATIC CALCIFICATION: STUDY OF CLINICAL AND ROENTGENOLOGIC DATA ON THIRTY-NINE CASES*

EARL E. GAMBILL AND DAVID G. PUGH

By the term "pancreatic calcification" we refer to calcareous deposits in the pancreas, either within the ducts or in the parenchymatous tissue outside the ducts or in both. From a practical clinical standpoint the inclusive term "pancreatic calcification" seems preferable to the term "calculi." Accordingly we have refrained from using the word "calculi" in order to avoid the possible implication that calcific deposits are necessarily located within the ducts.

Pancreatic calcification was apparently first reported by Graaf in 1667. Haggard and Kirtley in 1930 reviewed the incidence for a period of 271 years and could find authentic records of only 204 cases. Mayo reported on 25 proved cases of pancreatic calculi at the Mayo Clinic prior to 1930. That this complication of pancreatic disease is being recognized with increasing frequency is evidenced by the fact that prior to 1925, 102 cases were reported, whereas from 1925 to 1942 inclusive, 118 cases were reported in the literature. Snell and Comfort have also pointed out the fact that pancreatic calcification is being recognized with increased frequency.

OBJECTIVES AND PLAN OF STUDY

The objectives of the present analysis were (1) to study the symptomatology and the roentgenologic features in cases of pancreatic calcification and (2) to learn whether there is any correlation between the extent of calcification in the pancreas and the incidence of clinical manifestations, with particular reference to the manifestations of other complications of pancreatic disease such as diabetes mellitus and steatorrhea.

Evidence of pancreatic calcification is primarily a matter of roentgenologic diagnosis in the absence of surgical or postmortem examination of the pancreas since there are no symptoms or signs by which calcification can be diagnosed. In view of this fact we studied the roentgenographic and clinical features of those patients who, on roentgenologic examination, were found at the Mayo Clinic in the years 1939 to 1943 inclusive, to have pancreatic calcification.

* From the Archives of Internal Medicine (In press)

ANALYSIS OF DATA

Relation between Calcification and Pancreatitis.—There were thirty-nine cases in which, in the opinion of one of us (D. G. P.), the criteria for the roentgenologic diagnosis of pancreatic calcification were fulfilled. When the records of these thirty-nine cases were studied it was found that, with reference to the diagnosis of pancreatitis, the patients could be conveniently divided into four groups; namely, (1) those who had proved pancreatitis, (2) those who had probable but unproved pancreatitis, (3) those who had possible pancreatitis and (4) those who had no symptoms at any time which were, in any way, suggestive of pancreatitis (table 1).

TABLE 1

INCIDENCE OF PANCREATITIS IN THIRTY-NINE CASES OF PANCREATIC CALCIFICATION

Group	Pancreatitis	Cases	
		Number	Per cent
1	Proved	22	56
2	Probable	4	10
3	Possible	8	21
4	Negative history	5	13

Although the criteria which were used for the diagnosis of pancreatitis in this series of cases have been described in previous reports, a brief summary of these criteria is indicated at this point. A diagnosis of relapsing pancreatitis is justifiable in the presence of recurrent severe attacks of pain in the upper part of the abdomen commonly lasting for hours or days and often requiring the administration of more than one hypodermic injection of opiate, provided other causes for such attacks have been excluded and there is evidence of one or more of the following: (a) steatorrhea not otherwise explained, (b) pancreatic calcification on roentgenologic examination or at surgical exploration or necropsy, (c) supernormal concentration of amylase or lipase in the blood serum, (d) an enlarged, hard, nodular, edematous pancreas observed at surgical exploration and (e) leukocytic infiltration, interstitial fibrosis, residual necrosis, atrophy, calcification, pseudocysts and abscess formation in pancreatic tissue obtained for biopsy or at necropsy. Although pain is often severe and prolonged, this is not always true; in some instances pain may be relatively mild and atypical.

In this series of cases group 1 was made up of twenty-two cases or 56 per cent of the total. In nineteen of these twenty-two cases the diagnosis of pancreatitis was proved by the findings at operation or necropsy. In the three remaining cases of this group the criteria for the diagnosis of pancreatitis which were summarized in the preceding paragraph were satisfied.

Group 2 consisted of four cases or 10 per cent of the total and included those patients with probable, but not proved pancreatitis. In these cases

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there was a history of recurrent attacks of severe pain in the upper part of the abdomen which required opiates for relief, which were suggestive of pancreatitis and in which roentgenographic study of the gallbladder, stomach and duodenum failed to disclose in those organs evidence of disease sufficient to explain the pain.

Group 3, which consisted of eight cases or 21 per cent of the total, included those in which the histories were compatible with, but not typical of, that obtained in the usual case of pancreatitis. In four of the eight cases there was a history of acute severe pain in the upper part of the abdomen but the details were too poorly remembered to be of much clinical value. In the remaining four cases of this group there were complaints of pain in the upper part of the abdomen which were related particularly to alimentation but not diagnostic of pancreatitis. Flatulent dyspepsia and, at times, anorexia and nausea were experienced.

Group 4, which was composed of five cases or 13 per cent of the total, comprised those patients who gave no history suggestive of pancreatitis. One patient complained of mild pain and soreness in the right upper part of the abdomen which were relieved by lying down or by sitting. None of the other four patients of this group gave any history of abdominal pain. Gaseous dyspepsia and constipation were noted by two patients. One must keep in mind the possibility that the patients in this group could have had one or more relatively mild, unremembered episodes of acute pancreatitis in early life. Another possibility is that calcium had been deposited in the pancreas of these persons in response to a low-grade, subclinical pancreatitis in a manner analogous to that of the deposition of calcium in the lung or lymph nodes in tuberculosis.

It would appear from these findings that pancreatic calcification is usually, but not necessarily always, associated with a history of pancreatitis.

Sex.—Of the thirty-nine patients, twenty-eight or 72 per cent were males and eleven were females, a ratio of 2.5:1.0. The predominance of males over females has been observed also in chronic pancreatitis in which a ratio of 4.3:1.0 was noted in fifty-six cases.

Age.—In the thirty-nine cases of pancreatic calcification of this series the median age at the time that calcification was first discovered was forty-three years, the youngest age was ten years and the oldest, seventy years.

In twenty-one of the twenty-two cases of proved pancreatitis in which data were available, the median age at which seizures first appeared was thirty years, the youngest age, ten years and the oldest age, sixty-five years. Thus in one half of the cases the painful seizures began before the patient was thirty years old.

Weight.—Patients were of approximately normal weight for their height and age. Those who suffered from frequent severe episodes of pain and in whom diabetes mellitus or steatorrhea developed frequently lost between 15 and 20 per cent of their original weight.

Painful Seizures Associated with Pancreatic Calcification.—*Precipitating Causes.*—The possible influence of trauma, exercise and alcohol in the precipitation of the attacks of pain of pancreatitis has been discussed in previous studies. In one case of proved pancreatitis the first attack of pain came while the patient was playing baseball. These attacks continued to recur two to four times a year. Pancreatic calcification was discovered

the epigastrium, whereas when the calcification was present throughout the pancreas the pain more often than not was felt first in the epigastrium. While in some cases pain was confined to the initial or primary site, in many it was also propagated to other regions so that in most cases the entire upper region of the abdomen became involved.

TABLE 3
COMPLICATIONS ASSOCIATED WITH PANCREATIC CALCIFICATION

Complication	Cases	
	Number*	Per cent*
Diabetes mellitus .	9	23
Pancreatic steatorrhea	7	18
Gastro-intestinal hemorrhage	3	8
Morphinism	3	8
Inflammatory pancreatic pseudocyst	2	5
Pancreatic abscess.	1	3
Peripheral neuritis	1	3

* Based on thirty-nine cases of pancreatic calcification.

TABLE 4
INCIDENCE OF DIABETES AND STEATORRHEA IN THE PRESENCE OF PANCREATIC CALCIFICATION WITH AND WITHOUT A HISTORY OF PANCREATITIS*

History of pancreatitis	Cases	Diabetes		Steatorrhea	
		Cases	Per cent	Cases	Per cent
Positive	22	9	41	7	32
Negative or doubtful . .	17	0	0	0	0

* Based on thirty-nine cases of pancreatic calcification.

Associated Complications.—Complications which were found in association with pancreatic calcification were diabetes mellitus, steatorrhea, gastro-intestinal hemorrhage, morphinism, pancreatic pseudocyst, pancreatic abscess and peripheral neuritis (table 3).

Diabetes Mellitus and Steatorrhea.—In five cases of the ten in which diabetes developed the disease appeared within three years after the onset

of painful seizures. Occasionally diabetes mellitus or steatorrhea did not appear until after many years of recurrent attacks of pancreatitis. While it is doubtful whether calcification, as such, has much to do with the development of diabetes, yet proof is lacking to substantiate this doubt. The destruction of the islet tissue by repeated attacks of acute inflammation with or without necrosis would seem to be a more reasonable theory for the causation of such instances of diabetes.

The incidence of diabetes or steatorrhea or both in cases of pancreatic calcification was much greater among those patients who gave a positive history of pancreatitis than among those who gave a negative or doubtful history of pancreatitis. As a matter of fact, in this series diabetes or steatorrhea or both occurred only in those cases of calcification in which there was an associated history of pancreatitis (table 4). The evidence indicates, therefore, that when calcification is found in a case of chronic relapsing pancreatitis, it is prone to be associated with serious impairment in pancreatic function indicative of advanced disease. On the contrary, pancreatic calcification which is discovered accidentally or otherwise in a person who gives no previous history or a questionable history of pancreatitis is generally not prone to be associated with any gross disturbance in pancreatic function.

As might be anticipated, there seemed to be a high degree of positive correlation between the extent of calcification in the pancreas and the incidence of diabetes and steatorrhea. Thus in twenty-three cases in which the calcification was limited to the head of the pancreas only four instances of diabetes or steatorrhea occurred, whereas in eleven cases in which calcification involved the entire pancreas nine instances of diabetes or steatorrhea occurred.

It should be emphasized, however, that extensive pancreatic calcification is not always associated with signs of pancreatic insufficiency as is illustrated by one case (fig. 21). This patient suffered from one attack of pain suggestive of gallstone colic ten years before admission to the clinic. There had been no indigestion for seven years prior to admission. The cholecystogram was negative for disease of the gallbladder but revealed pancreatic calcification. There were no symptoms or signs of pancreatic insufficiency; however, no tests were performed to detect any possible subclinical deficiency.

There appeared to be no positive correlation between the size, shape or method of grouping of the calcareous deposits and the degree of pancreatic insufficiency. Moreover, the extent of calcification and the degree of disturbance of pancreatic function were not necessarily related to the length of time during which a patient had been suffering from the severe seizures of pain of pancreatitis.

Gross Gastro-intestinal Hemorrhage.—Gross bleeding from the upper part of the gastro-intestinal tract in the absence of demonstrable peptic ulceration or other gross lesions of the esophagus, stomach, duodenum, or liver has been observed in patients who have pancreatitis. Because of the frequent occurrence of the factor of alcoholism, it has been suspected that such bleeding may possibly be due to alcoholic gastritis. In this series of thirty-nine cases of calcification, three patients have a history of gross hemorrhages from the upper part of the gastro-intestinal tract. One patient suffered from recurrent gross hematemesis. He used alcohol chronically.

Physical, roentgenographic and gastroscopic examinations gave negative results. At exploration the surgeon found chronic pancreatitis but no evidence of any lesion of the stomach or duodenum.

Another patient suffered from recurrent hematemesis and melena. He likewise was a heavy user of alcohol. Roentgenograms of the stomach and duodenum were negative. At exploration the surgeon found severe chronic pancreatitis with pancreatic pseudocyst and abscess in the lesser peritoneal sac but found no gross lesions of the stomach or duodenum.

The third patient, who had severe chronic pancreatitis with diabetes and steatorrhea, had become addicted to the use of alcohol and morphine. While residing in a narcotic hospital in an effort to get rid of the addiction



Fig 21—Possible pancreatitis. Extensive calcification throughout the pancreas

to opiates, he experienced a gastro-intestinal hemorrhage which was fatal. Necropsy revealed that a spicule of calcium in the head of the pancreas had apparently eroded through the duodenum, thus causing the fatal hemorrhage.

Morphinism.—While morphinism is not strictly a complication specific for pancreatitis, it may result from the use of morphine for relief of the frequent exacerbations of severe pain due to pancreatitis. Consequently it may be difficult for the clinician to assess how much of the syndrome is due to results of addiction to morphine and how much to pancreatitis. In this series of thirty-nine cases of pancreatic calcification there were definitely two, and probably three, patients who were addicted to opiates. Two of

these patients had to go to an institution because of such addiction which had been induced by use of opiates for relief of the frequent and severe attacks of pancreatitis.

Pancreatic Pseudocysts.—In this series of thirty-nine cases of pancreatic calcification two pseudocysts occurred. They appeared to be the result of acute pancreatitis with necrosis and not secondary to calcareous deposits within the ducts.

Pancreatic Abscess.—In one case of this series two abscesses were observed in the tail of the pancreas at necropsy. These were the result of acute pancreatitis with necrosis. In another case, as a result of acute pancreatitis with necrosis, an abscess developed in the lesser peritoneal sac.

Peripheral Neuritis.—Peripheral neuritis developed in one patient who also had pancreatic calcification, diabetes mellitus and steatorrhea as complications of chronic pancreatitis. The exact etiologic basis for the neuritis in this case was not clear, although it appeared to be largely the result of severe malnutrition and diabetes.

Roentgenographic Aspects.—Calcareous deposits in the pancreas are almost always rather dense and, therefore, radiopaque. For this reason the roentgenologic diagnosis can be made with accuracy and the clinical diagnosis is dependent on this fact. In many instances it is the repeated painful seizures that eventually lead to the suspicion of pancreatitis and to the discovery of pancreatic calcification. Frequently the clinician may suspect the presence of gallstones and may make a cholecystogram only to find a normally functioning gallbladder and calcification in the pancreas. Occasionally pancreatic calcification is accidentally discovered at the time of roentgenologic study of the stomach, duodenum or colon. Roentgenographic study of the kidneys or lumbar vertebrae may commonly disclose the presence of unsuspected pancreatic calcification. It is in the unsuspected group that the diagnosis of calcification is most important, since such a diagnosis may direct attention to pancreatic disease that might otherwise remain unrecognized.

Any roentgenograms that include all or part of the pancreatic region may reveal calcareous deposits. In this series the deposits were seen most frequently, perhaps, in cholecystograms (fig. 22) or in localized roentgenograms of the gallbladder region (fig. 23). They were also discovered during roentgenologic examination of the gastro-intestinal tract. In some instances roentgenograms of the abdomen or of the urinary tract revealed their presence (figs. 24 and 25). In roentgenograms of the lumbar vertebrae they were seen not only in the anteroposterior projection but also in the lateral and oblique views (fig. 25). If the presence of pancreatic calcareous deposits is suspected, localized anteroposterior, oblique and lateral roentgenograms centered over the first and second lumbar vertebrae are most helpful. The pancreas varies somewhat in its location depending on the patient's habitus, but in this series calcareous shadows were seen most frequently at the level of the first and second lumbar vertebrae. At times they were seen as high as the level of the eleventh thoracic vertebra or as low as the level of the third lumbar vertebra. Calcification was present in various sites in the pancreas but it was seen most frequently in the head just to the right of the spinal column (figs. 22 and 23). At times calcification was situated in the head or body of the pancreas overlying the vertebrae and thus calcific

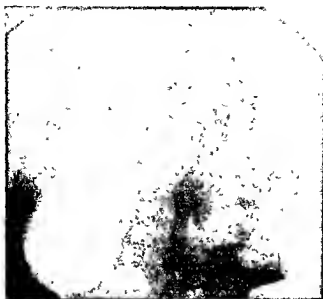


Fig. 22 — Possible pancreatitis. Irregular dense calcareous deposits in head of pancreas. Normally functioning gallbladder.



Fig. 23 — Proved pancreatitis. Calcification in the head and part of the body of the pancreas.



Fig 24.—Proved pancreatitis. Calcification throughout pancreas

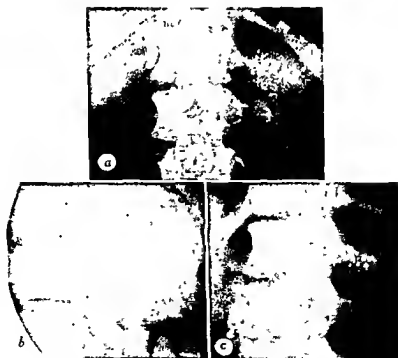


Fig 25.—Proved pancreatitis. *a*. Extensive calcification, especially in tail of pancreas. *b* Lateral view. *c*. Oblique view.

shadows were occasionally difficult to see. Oblique and lateral roentgenograms were of assistance in such cases (fig. 25). It is important that the roentgenograms cover the entire pancreatic region since otherwise small, localized shadows of calcification, particularly if situated in the tail of the pancreas, may be missed. In a few cases there was extensive calcification throughout the gland from head to tail, and in such cases the shape of the pancreas was well shown in the roentgenograms (figs. 21, 24 and 26).

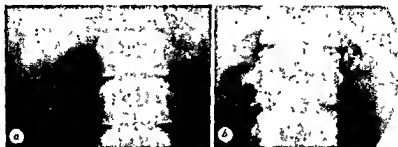


Fig. 26.—Proved pancreatitis. *a*. Cholecystogram in 1935 revealed no pancreatic calcification and a functioning gallbladder. *b*. Calcification throughout the pancreas in 1940.

Deposits of calcium in the pancreas varied greatly in shape and size (fig. 23). In some cases they were tiny, being only a few millimeters in diameter. Numerous small calcific shadows of this type were usually present when there was extensive involvement of the entire gland. Larger, well-circumscribed deposits were encountered; these occurred most commonly in the head or body of the pancreas. Shadows of calcification were sometimes seen which had the appearance of irregular, conglomerate masses of calcium. In rare instances, very large calcareous shadows, at times several centimeters in diameter, were seen. The finding of faceted stones in the duct of Wirsung has been reported but this is extremely unusual. Calcareous deposits of different shapes and sizes were often seen in the same gland.

In some instances the roentgenologic diagnosis of pancreatic calcification can be made with ease because of the location, size, shape and density of the calcareous deposits. However, other conditions which produce calcific shadows in the upper part of the abdomen must be differentiated from pancreatic calcification. Gallstones are frequently faceted, are more laterally situated and are not often so densely calcified as are calcific deposits in the pancreas. Occasionally in the cholecystogram the gallbladder appears to overlies the vertebrae; it is possible that gallstones in a gallbladder located in that position might resemble calcareous deposits in the pancreas. Stones in the common bile duct could be difficult to distinguish from calcific shadows in the pancreas, but the former are seldom densely calcified. Renal calculi are seen somewhat lateral to the pancreatic region. It is conceivable that renal calculi in a horseshoe kidney could be mistaken for pancreatic calcification. Calcified mesenteric nodes in the region of the head of the pancreas may be difficult to distinguish from calcification within the pancreas but as a rule the so-called mulberry appearance of calcified nodes and their presence in other parts of the abdomen make possible the correct

diagnosis. Calcification of the suprarenal gland can usually be identified by its location and shape.

Calcification of the abdominal aorta is linear and can be easily identified in the lateral view. Calcification of the arteries of the celiac axis is seen as linear, crescentic, or annular shadows of calcification. Localized calcification of the vertebral ligaments or calcification of the nucleus pulposus may be seen at the level of the head of the pancreas, but these should cause no confusion. At times special examinations, such as cholecystography and excretory urography, are necessary before a definite diagnosis can be made. Roentgenologic study after filling the stomach and duodenum with barium will aid in showing the relationship of calcareous shadows to the pancreatic region. However, special studies of this type are seldom necessary.

Treatment.—The indications for treatment of pancreatic calcification are primarily those employed for the treatment of pancreatitis, which we believe is the most common precursor of calcification.

Medical treatment seems to have little effect in preventing the painful exacerbations or in arresting the progress of the disease. A bland diet relatively low in fat, the abstinence from alcoholic excesses and the avoidance of excessive nervous and physical stress were advised, but there was no real evidence that these measures had any effect in reducing the frequency of occurrence or the severity of painful seizures. Whenever indicated, insulin was employed for diabetes mellitus and pancreatin for pancreatic steatorrhea. The cases of diabetes were relatively mild. In instances of steatorrhea it was noted that the amount of fat lost in the feces could be materially reduced by the use of pancreatin in appropriate amounts, usually from 2 to 10 gm. three times a day. There were nine cases of diabetes mellitus and seven cases of steatorrhea. In twenty-one of the thirty-nine cases operation was not performed.

For those who are afflicted with frequent attacks of severe pain, surgical intervention is the treatment of choice, although it is not always effective in stopping the attacks of pain and the results in a given case are unpredictable. Surgical intervention occurred in eighteen of the thirty-nine cases of this series for one or more of the following reasons: (1) to arrest the progress of the disease, or at least to try to reduce or abolish the frequency of occurrence and the severity of the painful seizures, (2) to relieve obstruction of the duodenum or common bile duct due to an enlarged pancreas, (3) to remove calcareous masses which might possibly be obstructing the exit of the main pancreatic duct and (4) to drain or remove pseudocysts or abscesses of the pancreas. While any type of treatment may give discouraging results and while the effectiveness of any given treatment is unpredictable, about two fifths of the patients who suffered from recurrent attacks of pain were completely relieved and about one fifth were partially relieved of the acute seizures for significant periods of time after certain surgical procedures designed to promote prolonged internal or external drainage of the common bile duct had been carried out. These procedures were cholecystogastrostomy, cholecystojejunostomy, choledochoduodenostomy and external drainage of the common bile duct by means of a T tube for at least six to twelve months. Of these, we are inclined to favor prolonged T tube drainage or, preferably, choledochoduodenostomy when that operation is feasible.

Pancreatolithotomy was performed in one patient, the surgeon removing some calcareous masses in and around the exit of the major pancreatic ducts. This procedure, followed by roentgen therapy over the pancreatic region, resulted in cessation of the painful seizures. Partial or total pancreatectomy was not employed in any of the cases of this series. We doubt that such procedures are justifiable except for patients who have severe and irreparable pancreatic insufficiency and who are invalidated by intractable pain.

End Results.—No immediate surgical deaths occurred among the eighteen cases in which operation was performed. One patient died, approximately three years after leaving the clinic, of a subhepatic abscess which was thought to be secondary to leakage at the site of cholecystogastrostomy which had been done previously for pancreatitis. Another patient, a non-surgical one, died a month after leaving the clinic. Necropsy was reported to show chronic pancreatitis with calcification, two abscesses in the pancreas and acute vegetative endocarditis. A third patient died of a massive gastro-intestinal hemorrhage as the result of erosion through the wall of the duodenum by a spicule of calcium in the pancreas.

In a few cases spontaneous amelioration of the painful seizures occurred, in others the disease progressed in spite of all efforts by the clinician and surgeon. In still others the severity of the disease did not change. Some patients became almost incapacitated for work, undernourished and addicted to opiates. Others turned to alcohol for spurious relief of what seemed to be a hopeless plight. The necessity for frequent hospitalization, numerous surgical operations and payment of medical bills and the inability to work constituted a serious economic, mental and emotional strain which sapped the morale of some of the patients with pancreatic calcification.

SUMMARY

In a study of thirty-nine cases of pancreatic calcification, selected solely on the basis of roentgenologic evidence of calcification, it was found that calcareous deposits in the pancreas were usually, but not always associated with relapsing pancreatitis. Commonly the symptomatology was that of pancreatitis, although in approximately two fifths of the cases there was either a negative or doubtful history of pancreatitis. Among those cases in which a definite history of pancreatitis was obtained, calcification became evident in a fifth of the cases in one year after onset of pain, but in another fifth of the cases calcification was not discovered until eleven to twenty-two years after onset of pain.

Associated complications in order of frequency of occurrence were diabetes, steatorrhea, gastro-intestinal hemorrhage, morphinism, pancreatic pseudocyst, pancreatic abscess and peripheral neuritis.

There was a high degree of positive correlation between the extent of pancreatic calcification and the incidence of two other complications associated with pancreatic calcification; namely, diabetes and steatorrhea. Diabetes and steatorrhea occurred only in those cases of calcification in which there was a definite diagnosis of pancreatitis.

EFFICIENCY OF GASTRO-INTESTINAL TRACT AFTER RESECTION OF HEAD OF PANCREAS*

ERIC E. WOLLAEGER, MANDRED W. COMFORT, O. THERON CLAGETT AND
ARNOLD E. OSTERBERG

By means of intake-excretion studies using standard test diets we have assessed the degree of impairment of the digestive and absorptive functions of the gastro-intestinal tract brought about by the surgical procedure necessary for resection of the head of the pancreas. When the pancreatic ducts were ligated at the time of operation, thus preventing the flow of pancreatic juice into the gastro-intestinal tract, impairment of gastro-intestinal function was invariably great. It was reduced in some patients by anastomosing the remaining portion of the pancreas to the small intestine. It was also reduced when pancreatin was administered.

An increase in the dietary fat and protein of these patients resulted in an increased wastage of fat and protein in the feces. An increase of dietary protein resulted in considerable increase in the amount of protein assimilated, while an increase of dietary fat resulted in a relatively small increase in the amount of fat assimilated.

By taking diets high in calories, protein and carbohydrate and low in fat, and by taking pancreatin if impairment of gastro-intestinal function was great, most patients who had undergone resection of the head of the pancreas were able to maintain a satisfactory nutritional status.

PRIMARY IDIOPATHIC SEGMENTAL INFARCTION OF THE GREATER OMENTUM†

CHARLES S. JOSS AND JOSEPH HYDE PRATT

The infrequent occurrence of primary idiopathic segmental infarction of the greater omentum was revealed when, in a review of the available literature, only twelve authentic instances of the condition could be found (tabulation). We wish to report such a case in which the lesion was seen at the Mayo Clinic recently.

REPORT OF A CASE

A white housewife forty years old was referred to the clinic on January 10, 1943, because of abdominal pain in the right lower quadrant of forty-eight hours' duration. Review of her history disclosed that she had been married twenty years, had been pregnant three times and had been delivered normally in each instance. She had made one previous visit to the clinic in the preceding year, at which time a diagnosis of "cardiospasm with moderate dilatation of the esophagus" had been made and dilatation of the cardia had been carried out. Her menstrual history was characterized by regular periods with a twenty-one day interval, and her last menstrual period had occurred three months before the onset of the present illness. The family history was irrelevant to her condition.

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† Abridgment of paper published in full in *Minnesota Medicine*. (In press).

TABULATION

PRIMARY IDIOPATHIC SEGMENTAL INFARCTION OF THE GREATER OMENTUM
CASES REPORTED IN LITERATURE

Reported by	Patient		Leukocytes, per cu. mm.	Diagnosis		Course
	Age	Sex		Preoperative	Postoperative	
Johnson, 1932	37	M	13,100	Acute appendicitis	Hemorrhagic infarct of omentum	Recovered
Pines and Hahnovitch 1949	31	M	18,400	Acute appendicitis	Infarct of omentum	Recovered
	33	F	10,000	Acute appendicitis	Infarct of omentum	Recovered
	40	M	16,000	Acute appendicitis	Infarct of omentum	Recovered
	32	M	23,300	Acute appendicitis	Infarct of omentum	Recovered
	37	M	8,800	Acute appendicitis	Infarct of omentum	Recovered
	37	F	8,000	Acute appendicitis	Infarct of omentum	Recovered
Bang-Denckhausen, 1941	46	F	Not recorded	Acute appendicitis	Hemorrhagic infarct of omentum	Recovered
Totter, 1947	27	M	Not recorded	Acute appendicitis	Hemorrhagic infarct of omentum	Recovered
	23	M	15,500	Perforated duodenal ulcer or perforated acute appendicitis	Hemorrhagic infarct of omentum	Recovered
Durando, 1943	38	F	Not recorded	Acute appendicitis	Hemorrhagic infarct of omentum	Recovered
MacKenzie and Small 1949	24	M	17,200	Acute appendicitis	Hemorrhagic infarct of omentum	Recovered
Present Author	41	F	15,800	Acute appendicitis Pregnancy	Infarct of omentum Pregnancy	Recovered

Two days before the patient's entry, abdominal pain had developed in the right lower quadrant whenever the patient arose. This pain was constant, nonradiating, and was not accompanied by nausea. The pain persisted throughout the day, although the patient was ambulant, her appetite was good, and her distress was not too annoying. During the night of the date of onset of the pain she occasionally was awakened by the abdominal pain. On the next day the abdominal pain continued to be steady, sharp and nonradiating, in the right lower quadrant of the abdomen. The patient had regular bowel movements and had noted no other symptoms except that the pain seemed to be worse on motion of the body. On the day of her admission the patient had been seen by her local physician, who had made a diagnosis of "acute appendicitis" and had referred her to the clinic for treatment.

Physical examination revealed a well-developed and well-nourished white woman who was apprehensive and crying. Her systolic blood pressure was 128 mm. of mercury, the diastolic pressure was 76 mm. of mercury. Her pulse rate was 90 beats per minute. Her temperature at admission was recorded as being 98° F. (37° C.) Abdominal examination disclosed point tenderness of grade 2 (on the basis of 1 to 4, in which 4 is most severe) in the right lower abdominal quadrant, and voluntary spasm and rebound in the same area. Vaginal examination revealed the cervix to be soft and freely movable. The uterus was felt to be the size of a uterus two to three months pregnant. The adnexa appeared to be normal. Rectal examination revealed slight tenderness of the right lateral wall. Results of the remainder of the examination were within normal limits.

Examination of a catheterized specimen of urine revealed it to have a specific gravity of 1.016. Albuminuria of grade 1 (on a basis of 1 to 4) was present. Microscopic examination of the sediment of a specimen of centrifuged urine disclosed an occasional erythrocyte and ten leukocytes per field, under low-power magnification. White blood cells numbered 15,000 per cubic millimeter; 82 per cent were polymorphonuclear neutrophils, 16 per cent were lymphocytes, 1 per cent were monocytes and 1 per cent were eosinophils.

The preoperative diagnosis was probable atypical acute appendicitis as well as intra-uterine pregnancy. Surgical exploration was advised and accepted.

Abdominal exploration, through a primary lower right rectus incision, was carried out on the day of the patient's admission. Spinal anesthesia with procaine hydrochloride was employed. A portion of the greater omentum 3 by 3 cm. was found to be the site of an acute inflammatory reaction, and was excised. The remainder of the abdominal exploration disclosed nothing significant except for the enlarged uterus, which extended well above the symphysis pubis, was rather soft, and seemed to contain a normal fetus. The appendix was removed and the abdomen was then closed. Five grams of crystalline sulfathiazole was left in the peritoneal cavity.

Microscopic examination of the excised omental tissue disclosed infarcted omentum. The appendix showed signs of chronic inflammation.

Convalescence was uneventful. The patient was dismissed from the hospital on the twelfth postoperative day, at which time she had no complaints.

COMMENT

Review of the cases of primary idiopathic segmental infarction of the greater omentum in the literature does not reveal any significant features which might be of aid in a definite, preoperative differential diagnosis between the lesion and acute appendicitis or other acute intra-abdominal lesions. Undoubtedly, this type of infarction of the omentum occurs more frequently than is indicated by the number of reported cases. In many instances it probably is not recognized because of the inability of the surgeon to carry out thorough exploration of the abdomen when a small McBurney incision has been made with the expectation that the pathologic process is situated in the appendix or terminal portion of the ileum. It is not unlikely that a small percentage of patients thought to have "acute appendicitis" which is atypical and consequently is treated by medical measures, in reality have infarction of the greater omentum. We wish to add our voice to that of others who have suggested that this pathologic entity should be considered whenever surgical exploration fails to reveal pathologic changes in the appendix or other suspected organ or structure to account for the clinical symptoms, and that the omentum be inspected for evidence of a lesion or lesions which might explain such symptoms.

The course of infarction of the greater omentum not treated surgically undoubtedly is benign. When operation is not performed the omentum probably adheres to adjacent organs or structures. Such early, fine adhesions between omentum, parietal peritoneum and bowel have been found at operation in cases of segmental infarction of the greater omentum.

AN UNUSUAL COMPLICATION OF A MECKELIAN DIVERTICULUM*

CARL G. MORLOCK AND JAMES G. BENNETT

The persistence of the vitello-intestinal duct in man, in whole or in part, is variously estimated to occur in from 1 to 2 per cent of instances. The early human embryo is imperfectly differentiated from a large and conspicuous yolk sac and communicates with this sac widely by its ventral surface. This communication forms the lumen of the vitelline duct; it is conspicuous during the first month of gestation, but it usually disappears by the sixth or seventh week of fetal life. In cases in which the closure and obliteration of the vitelline (umbilical) duct are imperfectly effected before

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birth, a portion, or even all of the duct may persist as a pervious tube. The anomaly caused by a persistent vitelline duct is termed "Meckel's diverticulum." The vitelline duct is accompanied in the embryo by the umbilical vessels. The latter, like the duct itself, may persist and in adult life may be found close to the diverticulum; they may have an independent course or they may lie along the free border of the mesentery of the diverticulum.

We recently had the opportunity of seeing a patient in whom an external fecal fistula, secondary to Meckel's diverticulum, developed late in life. Because of the unusual nature of the case and the difficulties presented in diagnosis we felt it would be worth while to report it.

REPORT OF CASE

A seventy-five year old widow had always been in good health except for a moderate hypertension of many years' duration. She had undergone cholecystostomy for cholelithiasis thirty years before admission to the clinic and had recovered therefrom without incident. Four days prior to admission, after the patient had played rather strenuously with her young grandson, generalized crampy abdominal pain, followed by vomiting and moderate distention of the abdomen developed. She consulted her family physician, who performed a roentgenologic examination of the stomach and colon and found them normal. She became progressively more ill and was referred to the clinic for an opinion.

At the time of admission the patient was very ill, toxic and dehydrated. The tongue was dry and furred. The blood pressure was 170 mm. of mercury systolic and 100 mm. diastolic. Examination of the chest revealed depression of breath sounds, with fine crepitant rales at the base of the right lung. The abdomen was distended and moderately tympanitic; few peristaltic sounds were audible. About the umbilicus was a red indurated area of cellulitis which measured approximately 3 inches (7.5 cm.) in diameter, with an area of subcutaneous crepitus at its upper edge. The clinical picture was that of ileus with complicating bronchopneumonia. It was difficult to account for the periumbilical cellulitis.

The voided urine contained albumin, grade 2 (on the basis of 1 to 4, in which 1 represents the mildest, and 4 the most severe condition), numerous hyaline and a few granular casts, and a few erythrocytes and leukocytes. The Kline flocculation test of the blood serum gave a negative result. The hemoglobin measured 14.6 gm. per 100 c.c. of whole blood and the leukocytes numbered 6,000 per cubic millimeter. The value for blood urea was 14.1 mg. per 100 c.c. and for the serum chlorides, 534 mg. per 100 c.c. A roentgenogram of the chest showed pulmonary congestion and beginning bronchopneumonia on the right side. A roentgenogram of the abdomen revealed some distention of the coils of the small intestine.

Food could not be retained because of nausea, so fluids were given intravenously. Because of the pneumonia, 2.5 gm. of sodium sulfadiazine were given intravenously every day. The abdominal distention was relieved by intestinal intubation.

Despite every supportive measure available, the patient became progressively more ill. There was persistent fever, with a temperature which varied between 101° and 103° F. (38.5° to 39.4° C.). The pneumonia became more extensive. Necrosis and ulceration developed in the area of periumbilical cellulitis and foul purulent material, with a strongly fecal odor, began to drain from this point on the third hospital day. Death ultimately occurred on the sixth hospital day.

At necropsy we found a small opening at the umbilicus from which was oozing thin purulent fluid with a fecal odor. On opening the peritoneal cavity no evidence of inflammation was noted. A bandlike structure arose from the ileum 15 cm. proximal to the ileocecal valve and extended to an attachment at the umbilicus. This appeared to be a persistent vitello-umbilical duct (Meckel's diverticulum).

There was abnormal mobility of the cecum and ascending colon, these structures lying in the left half of the abdomen. There was chronic ulcerative cholecystitis with cholelithiasis. The gallbladder contained 150 c.c. of purulent fluid and five black stones which averaged from 0.5 to 0.6 cm. in diameter. Thrombosis of the left iliac and femoral veins had led to bilateral pulmonary embolism, and small infarcts of the lung were present. Incidental findings were a traction diverticulum of the esophagus associated with healed tuberculosis of the lungs and hilar lymph nodes, and diverticulosis of the sigmoid. The immediate cause of death was considered to be extensive bronchopneumonia which had involved both lungs.

On closer examination, the Meckel's diverticulum was found to arise from the lumen of the ileum at an oblique angle, the proximal 4 cm. of it being incorporated in the wall of the ileum; both the diverticulum and the ileum were covered by a common serosa which, in effect, produced a double lumen tube. The opening into the ileum was approximately 1.3 cm. in its greatest diameter, and the average diameter of the proximal portion of the diverticulum was 0.8 cm. The length of the diverticulum, from its point of contact with the bowel wall to its junction with the anterior abdominal wall at the umbilicus, was 17 cm. The distal portion of the diverticulum, for a distance of 6 cm., ran parallel to the anterior abdominal wall and was covered by parietal peritoneum. The terminal 2.5 cm. of the diverticulum was gray in appearance and necrotic, but it was intact throughout, except for the tip. A fistulous tract began at the tip of the diverticulum, coursed through the subcutaneous fat and an abscess in the subcutaneous tissue, and opened externally at the midpoint of the umbilicus. The subcutaneous abscess contained approximately 4 c.c. of pus. There was no gross evidence of ulceration on the mucosal surface of the diverticulum proximal to its attachment to the anterior abdominal wall.

Microscopic examination of sections taken from the distal portion of the diverticulum showed chronic suppurative inflammatory changes with active proliferation of fibroblasts and capillary loops. Much of the mucous membrane of this portion of the diverticulum was destroyed. The lumen of the diverticulum was filled with polymorphonuclear leukocytes and necrotic debris, and it communicated freely through a necrotic diverticular wall with an abscess in the fibrous and adipose tissue of the anterior abdominal wall. Sections taken from the proximal portion of the diverticulum showed a minimal amount of acute inflammatory exudate on the serosal surface, otherwise they were not remarkable. There was no evidence, from any section taken, of generalized peritonitis. A section of the diverticulum at its junction with the anterior abdominal wall confirmed the gross impression that it was covered with peritoneum, this led to the conclusion that the diverticulum was congenitally located in the position in which we found it, and that it had not become secondarily attached as a result of an inflammatory process.

PRIMARY NONSPECIFIC ULCERS OF THE SMALL INTESTINE*

JOHN A. EVERT, B. MARDEN BLACK AND MALCOLM B. DOCKERTY

Nonspecific localized ulcerations of the jejunum and ileum are so similar pathologically as to justify their classification as a group under the name "primary" or "simple" ulcers. Although the lesions are characteristically solitary, small groups of ulcers are sometimes found. The etiology of primary ulcers is unknown. There is little direct evidence to support the theories that they are caused by infection, irritation from gastric secretions, trauma or vascular abnormalities.

The symptoms of primary ulcer are for the most part secondary to the complications of perforation, bleeding or obstruction. The possibility of these lesions should be considered in the presence of unexplained intestinal bleeding or of peritonitis which suggests acute visceral perforation when such perforation cannot be found in the stomach or duodenum.

The mortality rate in patients suffering from primary ulcer is high. The lesion has been recognized during life only after some complication has led to surgical intervention.

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REDUNDANT BLIND SEGMENTS OF INTESTINE FOLLOWING SIDE-TO-SIDE ANASTOMOSIS WITH DIVISION OF THE BOWEL: REPORT OF FIVE CASES*

B. MARDEN BLACK AND CECIL G. McEACHERN

The potential hazards associated with the inverted end of the proximal segment of bowel following division of the bowel and side-to-side anastomosis are dilatation and hypertrophy, ulceration and perforation.

Some dilatation and hypertrophy of the proximal end of the bowel distal to the anastomosis develops in many cases but symptoms are rarely produced.

When longer than usual lengths of the proximal segment are left distal to the anastomosis symptoms suggestive of partial obstruction may develop. The colicky pains occur in attacks and may be accompanied by vomiting and diarrhea.

Complications associated with the inverted end of the proximal loop are unusual as judged by the rarity of the reported cases and by the rarity of cases in our own series. They are largely preventable by avoiding redundant segments of the proximal end of the bowel distal to the anastomosis.

Such complications are so unusual that they do not detract from the usefulness of side-to-side anastomosis.

GRANULOMAS OF THE ILEOCECAL REGION SECONDARY TO APPENDICITIS (LIGNEOUS CECITIS) WHICH SIMULATE NEOPLASMS†

JAMES W. WILSON, MALCOLM B. DOCKERTY, JOHN M. WAUGH AND J. ARNOLD BARGEN

In a series of twenty cases of "ligneous cecitis" or "nonspecific appendiceal granuloma," most of the lesions were caused by perforative inflammatory disease of the appendix. Incomplete removal of the appendix was responsible for the lesion in two of the cases and an excessive amount of nonabsorbable suture was responsible in another.

The average age of the patients was 52.1 years. Their advanced ages probably accounts for the fact that their perforations were less acute than those usually seen.

The appendices were usually located in the ileocecal angle or in the retrocecal or retro-ileal regions, permitting the rapid sealing off of the appendiceal inflammation.

The tumor resulted from an extensive overgrowth of relatively avascular, inflammatory, fibrous tissue about the appendix after repeated attacks of low-grade inflammation.

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ient obstruction had led to decreased dietary intake. An earlier group of symptoms is related more to the existence of pelvic endometriosis than to its intestinal complications and these symptoms are herein mentioned to complete the picture on a chronic basis.

Infertility, relative or absolute, was frequently present and nine of the patients complained of absolute sterility. The ten married women in the series had had a total of but three pregnancies, only two of which terminated with the birth of live children. One of the four unmarried patients had had a pregnancy which terminated in (or was terminated by) abortion. Among the four women who had been pregnant the average period which had elapsed since the last pregnancy was 14.2 years with extremes of five and twenty-three years. The importance of these findings is further emphasized by the fact that six of the ten married patients mentioned had undergone previous pelvic operations designed in several instances to make pregnancy possible by resecting regions of endometriosis.

Acquired dysmenorrhea was a major symptom in eight of the sixteen cases. In an additional four cases the patients did not complain of this symptom. In the remaining four cases the records did not supply information on this point. Dyspareunia, surprisingly enough, was not listed as a major symptom by any patient in this group. It was elicited as not being a symptom in two cases and in the remainder the records were noninformative. However, five of the thirteen patients whose lesions were found in the lower segments of the bowel had complained of rectal pain and several others had complained of pain on defecation. Menstrual irregularities, so prominent in cases of pelvic endometriosis, were noted in only four of the cases. In nine the periods were described as being regular, two patients had undergone previous hysterectomy and one patient had been amenorrheic for three years as a consequence of the menopause. Menorrhagia was noted as a symptom four times among the group and two patients having otherwise normal menses had complained of some intermenstrual spotting.

The afore-mentioned symptoms, which were relevant to the underlying endometriosis rather than to its obstructive complication, had been present for periods varying from several months to eighteen years with an average duration of 6.5 years.

Physical findings in all sixteen cases were consistent with the clinical diagnosis of intestinal obstruction. On the basis of an evaluation of symptoms combined with the results of digital rectal and vaginal examination, the correct diagnosis was made preoperatively in seven of the sixteen cases studied.

Sigmoidoscopic examination was performed in twelve cases and in nine of these positive evidence of luminal narrowing was obtained. In two cases, as was proved later, the sigmoidal lesions were beyond the reach of the sigmoidoscope and in the third case in which the findings were negative the lesion was located in the terminal portion of the ileum. In none of the cases was the presence of mucosal ulceration observed. In several cases, however, the sigmoidoscopist remarked on the peculiar puckering of the mucosa over the area of involvement.

In nine of eleven cases results of roentgenographic study after administration of barium enemas were interpreted as being positive inasmuch as the roentgenograms demonstrated and localized the point of the obstruc-

tion. The two "failures" were in a case in which the lesion was ileal and in another in which the upper portion of the rectum was only mildly obstructed by the endometrioma. By way of offsetting these two cases the roentgenologist in two of the less "positive" examinations suggested the diagnosis of obstructing endometrioma.

TREATMENT*

Fifteen of the sixteen lesions were treated surgically by local resection of the bowel and in one instance partial excision of the endometrioma was accomplished. The details of the various procedures in the sixteen cases follow:

a. When the Point of Obstruction Was in the Sigmoid or Distal to It.—Resection of the bowel was done in twelve of the thirteen cases in this group and in one the endometrioma was excised. In five of the cases complete resection of a segment of the bowel was done and in one case the resection of the bowel was partial. In this group of twelve resections of the bowel colostomy was performed eight times and cecostomy was performed once. In two patients in their early thirties in this group myomectomy was performed plus resection of the bowel in a conservative effort to preserve reproductive function. Resection of the lower part of the bowel plus removal of both tubes and ovaries or of the remaining tube and ovary was done in five cases. Panhysterectomy plus resection of the bowel was done in one case and panhysterectomy plus partial excision of the endometrioma was done in one case.

b. When the Point of Obstruction Was in the Distal Portion of the Ileum.—Enterostomy plus ileal resection was done in one case. An initial Witzel ileostomy and a subsequent right hemicolectomy and ileotransversostomy were done in one case. Ileal resection plus ileocecostomy and removal of the remaining tube and ovary were done in one case.

Follow-up and Relief of Symptoms.—These patients had been followed up by examination and letters for from one month to twenty-one years. An excellent result with complete relief of the symptoms was obtained in twelve cases, a good result in two cases and a fair result in two cases.

Deaths.—There were no deaths.

PATHOLOGIC OBSERVATIONS

Pertinent gross pathologic observations noted on the fifteen resected lesions and the one partially excised lesion were as follows:

Nature.—Three sigmoidal lesions had produced obstruction by virtue of an annular or napkin-ring type of infiltration with more or less concentric narrowing of the intestinal lumen. In eight additional cases (two lesions classified as high rectal and six as sigmoidal) the appearance was that of polypoid submucosal infiltration producing obturation of the intestinal lumen. In two other instances an eccentric cicatrization produced by infiltrating endometriomas had produced acute angulation while at the same time submucosal proliferation of the endometrial tissue gave a superadded

* It is to be emphasized that most of the cases in the current series occurred before the time of the changing concept of treatment from that of resection of the bowel to that of bilateral oophorectomy. Present treatment consists in panhysterectomy plus conservative treatment of the bowel.

factor of obturation. A combination of impingement and kinking from endometrial adhesions obtained in the three cases of ileal endometrioma with obstruction.

Size.—Gross limits of the infiltrations varied from 6 by 4 by 2.5 cm. to 1 by 1 by 1 cm. The average dimensions were 2.5 cm. in diameter with seven of the endometriomas exceeding this size.

Color.—The dark red mottled appearance so characteristic of the lesions as seen at operation was replaced in the formalinized specimens by the presence on the peritoneal and cut surfaces of scattered bluish black spots



Fig 27.—Gross specimen (case 1) of terminal ileum, cecum, appendix and ascending colon. Note endometriosis causing obstruction at a point 5 cm. proximal to the ileocecal valve and the dilatation of the bowel above this point

on a whitish brown background of fibromuscular tissue. Some of the cut surfaces presented a striated appearance and from them tiny drops of brownish black fluid could be expressed by scraping with a knife.

Consistency, Mucosal-serosal Relations and so Forth.—The involved tissues were nodular, firm and fibrous without sharp delineation in the zones demarcating the edges of the infiltrations. In nine instances the overlying mucosa was puckered in a roset fashion, in six it was irregularly pitted and in one case it presented an edematous polypoid appearance. Although no gross mucosal ulceration was noted, in eleven of the sixteen cases the

mucosa was more or less firmly adherent to the underlying submucosa and to the muscularis propria. Irregular puckering of the peritoneal coat was noted in all of the lesions.

Proximal Segments.—In all of the specimens in which accurate luminal dimensions could be studied the bowel proximal to the obstruction showed the effects of stasis in the form of dilatation (fig. 27). In eleven cases this degree of dilatation was estimated to be two or more times the luminal diameters distal to the endometriomas. This obstructive dilatation, moreover, was paralleled in a general way by increases in thickness of the muscularis propria. In nine of the specimens this layer was approximately doubled in thickness.



Fig. 28.—Sigmoid (case 5). Endometrial glands and stroma are seen in the submucosa. Note variation between amount of glands and stroma present (hematoxylin and eosin $\times 65$).

Associated Pathologic Conditions.—Uterine fibromyomas had been noted at operation or removed in eight of the sixteen cases. Six patients had extensive ovarian endometriosis with tarry cysts. Four patients had simple ovarian cysts and the ovaries and tubes of an additional two were involved in adhesions. If in addition we consider that nine patients had previously undergone surgical exploration of the pelvis it becomes apparent that the obstruction of the bowel by endometriosis was but a part of the picture.

MICROSCOPIC FEATURES

In essence the intestinal lesions consisted in invasion by endometrial glands and stroma of the serosa, muscularis, submucosa and mucosa in

TABULATION

POSITION OF THE ENDOMETRIAL GLANDS AND STROMA IN ENDOMETRIOMA
OF THE BOWEL FROM THE CURRENT SERIES

Case	Segment of bowel	Submucosa		Muscularis		Serosa	
		Glands	Stroma	Glands	Stroma	Glands	Stroma
1	Ileum	+	+	+	+	+	+
2	Ileum	0	0	+	+	+	+
3	Sigmoid	+	+	+	+	0	0
4	Ileum	0	0	+	+	+	+
5	Sigmoid	+	+	+	+	0	0
6	Sigmoid	0	0	+	+	0	0
7	Sigmoid	0	0	+	+	0	0
8	Sigmoid	+	+	+	+	+	+
9	Sigmoid	+	+	+	+	0	0
10	Sigmoid	+	+	+	+	+	+
11	Rectosigmoid	+	+	+	+	+	+
12	Rectosigmoid	+	+	+	+	+	+
13	Sigmoid	+	+	+	+	+	+
14	Sigmoid (excision)	-	-	+	+	+	+
15	Rectosigmoid	+	+	+	+	+	+
16	Sigmoid	+	+	+	+	+	+

* + = positive, 0 = negative; - = not stated

variable combinations (tabulation). Added to this was the important factor of reactive fibrosis with stenosis resulting from the contraction of maturing fibrous tissue. Since the process was fundamentally extrinsic in point of origin, mucosal changes were the least frequently noted. In four instances the endometrial glands and stroma invaded the muscularis mucosae and in one of these a microscopic-sized area of ulceration involved the overlying epithelium. Considerable mucosal scarring was present. Infiltration of the submucosa obtained in eleven instances (fig. 28). All specimens showed infiltration of the muscularis propria. All three specimens of ileal endometriosis showed a major concentration of endometrial glands and stroma in the serosal and outer muscular coats. In contrast the sigmoidal and high rectal lesions were generally of the "deep" type—that is, the inner circular layer of muscle and the submucosa exhibited the greatest number of these

ectopic elements. As a matter of fact in five cases of well-circumscribed endometriosis of the sigmoid, routine sections failed to reveal the presence of serosal endometriosis, although one certainly might concede that it had existed earlier in the course of the invasive process.

Although the proportion of endometrial glands to stroma varied a great deal (fig. 28), in general these elements were present in about equal proportions. The glandular and stromal elements were in all cases similar to their normal intra-uterine counterparts and they exhibited pictures typifying all the phases of the menstrual cycle. Within the musculature of the bowel the endometrial glands seemed to proliferate in an axis parallel to that of the muscle bundles as though the invading tissue were following the lines of least resistance rather than permeating lymphatic spaces. The presence in six cases of cystic glandular hyperplasia was correlated with a clinical history of menstrual irregularity noted in the histories.

Studies made using the van Gieson stain for fibrous tissue revealed in all instances fibroblasts and collagenous fibrils around the nests of endometrial glands and atroma. This fibrous tissue was occasionally hyalinized. In both the fibrous and the hyalinized examples this reactive tissue was seen to infiltrate the invading glands and stroma on the one hand and the invaded muscular tissues on the other.

Stains for iron demonstrated the presence of this substance in five instances only. This was something of a surprise since we had surmised that the cicatrization would obtain on the basis of a reaction to hemosiderin deposited during "menstruation" from the ectopic endometrium.

COMMENT

Endometriosis is the only common condition in which there occurs invasion of one tissue by another normal tissue of the same host.*† When the bowel is the victim of this infiltrative process the segments affected are usually those which are situated in the pelvis. These are the sigmoid, the rectosigmoidal juncture, the rectum and the distal portion of the ileum. As with endometriosis elsewhere the survival of the lesions is predicated on the influence of the cyclic hormonal stimulation of the ovaries. In the absence of this stimulation endometriosis undergoes retrogression. Endometriosis invades the intestinal wall from its serosal side and grows inward into the muscular layers and the submucosa. Rarely may the mucosa of the bowel be invaded grossly.

The frequency with which the diagnosis of endometriosis is made by the clinician, the surgeon or the pathologist varies with their "threshold of suspicion" and it is our feeling that many cases have passed unrecognized.

The symptoms of intestinal obstruction caused by endometriosis may be divided into two main groups: (1) the symptoms and signs of usually extensive pelvic endometriosis and (2) the symptoms and signs of intestinal obstruction in its various degrees.

Endometriosis occurs in women usually between the ages of thirty and

* Traumatic rupture of the spleen is occasionally followed by a peritoneal seeding of splenic transplants.

† The placenta might be considered to be an exception, depending on the interpretation of the word "host."

fifty years. The majority of the women are sterile. More than half of the women have never been pregnant* and at least two thirds have never carried a fetus through to full term delivery.

A periodicity of symptoms associated with the menstrual cycle and the onset of menstruation is the single most important sign of endometriosis per se and its complication of intestinal involvement. This periodicity of symptoms includes both the symptoms of endometriosis and those of intestinal obstruction. A history of the symptoms of acquired dysmenorrhea, rectal pain associated with or between defecations, sacral pain or deep pelvic pain or discomfort (which may extend down into the thighs and is made worse by jarring), severe constipation or diarrhea, and dyspareunia that are increased just before, during or just after menstruation is usually indicative of extensive endometrial involvement of the sigmoid, rectosigmoidal juncture or rectum. When these symptoms become progressively worse and lengthen out in duration premenstrually, postmenstrually or both, obstructive intestinal symptoms are usually imminent.

The symptoms of intestinal obstruction then become superimposed on those of endometriosis of the bowel, at first usually only "comenstrually." These symptoms for the sigmoid and below are those of lower abdominal pain (which is one of the first to be present), along with abdominal distention, and finally obstipation, which may be present for only one or two days during the period. When the sigmoid or more distal portions of the bowel are obstructed, nausea and vomiting usually occur late because of the competence of the ileocecal valve. Occasionally a reflex type of nausea and vomiting may be encountered. The symptoms of the endometriosis plus the superimposed symptoms of the intestinal obstruction, which at first are mild, become progressively worse, lengthen out premenstrually or postmenstrually, and either go on to the production of acute complete or partial obstruction at one of the menstrual periods or assume the form of chronic intermittent partial obstruction of high or low grade.

Compared with intestinal obstruction in general caused by endometriosis ileal obstruction caused by endometriosis more often occurs among younger women, who usually have less extensive pelvic involvement by endometriosis or sometimes no other grossly visible pelvic involvement. These patients may or may not have the general symptoms of endometriosis, but when these symptoms are present it is usually to a lesser degree. This is represented by the facts that the group with ileal involvement had a higher fertility rate, fewer previous pelvic operations, fewer uterine fibroids and a lesser incidence of associated pelvic pathologic changes. Also in the ileal group no patient had rectal pain, constipation was less frequent, only one patient complained of diarrhea and no patient had blood in the stools. Vomiting was a more frequent symptom than obstipation.

Gross blood in the stools is usually not an important symptom of endometriosis of the bowel. It is of significance only when other anorectal lesions have been excluded and when it is present only at the menstrual period.

Valuable adjuncts to the symptoms in the diagnosis of intestinal obstruction as caused by endometriosis are digital examination of the vagina and rectum, the sigmoidoscopic examination, and roentgenographic examination

* This too may depend on the physician's "threshold of suspicion" in the search of the patient's past history.

of the colon and the terminal portion of the ileum after administration of a barium enema.

Pelvic examination most often reveals tender palpable nodules in the rectovaginal septum or the pouch of Douglas, frequently the presence of associated uterine fibroids and in many cases the presence of ovarian cysts, usually bilateral. On operation these are most often observed to be the chocolate cysts of endometriosis. Pelvic examination is best made just before or during menstruation because of increased tenderness and congestion. If a discrete endometrioma is present in the rectovaginal septum it may be palpated. A thorough search of the vaginal vault via a speculum at the time of menstruation may reveal the presence of the purplish pink lesions of endometriosis which have invaded the vaginal wall. The vaginal wall may sometimes be invaded but the rectal mucosa almost never is.

On sigmoidoscopic examination there is rarely gross bleeding and almost never gross ulceration. The positive findings will be those of a greatly narrowed lumen, an anterior extrarectal mass, acute angulation of the bowel and mucosal puckering and congestion. The appearance is much like that of obstructing diverticulitis and cannot be positively differentiated from it by means of the sigmoidoscope but the intact mucosa differentiates it from carcinoma. Biopsy of the intestinal mucosa is usually not practical, for, since the mucosa is not extensively involved, the report will usually come back "negative" or "inflammatory change only." Even in the few cases in which rectal bleeding has been a symptom, the mucosa has appeared only puckered or adherent, but not ulcerated, and fairly normal. It is important to remember that carcinoma invades the intestinal wall from the mucosa outward while endometriosis invades it from the serosa inward.

A roentgenologic examination of the colon is assuming a role of importance in the diagnosis of endometriosis causing intestinal obstruction. If the obstruction is complete the employment of a roentgenogram of the colon may accurately localize the lesion. If the obstruction is incomplete the proper interpretation of the roentgenogram of the colon may not only localize the obstructing lesion but identify the cause as endometriosis as well. The characteristic lesion on roentgenologic examination of the colon is said to be a long, inconstant filling defect with sharp regular borders, intact mucosa and fixation of the bowel, which is very tender to palpation.

Diagnosis.—The diagnosis of intestinal obstruction which has been caused by endometriosis or endometrioma may best be made by first obtaining an accurate history of the development of the symptoms which are diagnostic of endometriosis. Points of importance are as follows: (1) a woman in the reproductive period of life, usually between the ages of thirty and fifty years, (2) who is in fairly good general health and has not lost weight, (3) who suffers from absolute, relative or secondary sterility or who has married late or has not been pregnant for some time, (4) who has acquired dysmenorrhea, and (5) who has a history of usually a year or longer of symptoms which occur with menstrual periodicity; (6) symptoms, such as severe constipation, "rectalgia" or dyschezia, dyspareunia, occasionally diarrhea, and rarely rectal bleeding; (7) low deep pelvic discomfort caused by jarring of the body; (8) sacral backache which may run down into the thigh, and (9) symptoms of intestinal obstruction such as lower abdominal cramping colicky pain, abdominal distention and obstipation

or vomiting or both which have shown menstrual periodicity and become progressively more severe.

These symptoms plus the finding of: (1) on pelvic examination tender nodules in the pouch of Douglas or a large tumor of the rectovaginal septum and associated uterine fibroids and bilateral ovarian cysts, and (2) a sigmoidoscopic examination that shows an intact puckered mucosa and a stenosed or narrowed intestinal lumen from an extrarectal mass, or (3) a roentgenogram of the colon that shows a long, inconstant filling defect with regular borders, intact mucosa and fixation of a tender bowel indicate a highly presumptive diagnosis of intestinal obstruction caused by endometriosis. Positive diagnosis can be made only by operation and surgical biopsy of the lesion with frozen section and microscopic pathologic confirmation.

Treatment. 1. Surgical Treatment.—The treatment of intestinal obstruction caused by endometriosis is surgical. The basic principle in the treatment of this condition is the fact that retrogression of endometriosis depends on the absence of ovarian hormonal stimulation. Hence, to treat the patient the surgeon may elect usually to remove both ovaries* (as pointed out by Milnor and others) or occasionally to resect the bowel or in rare instances to do both. Factors to be considered by the surgeon are the age of the patient, her desire to become pregnant, the probability of her becoming pregnant, the existence of associated pelvic pathologic lesions and the location and extent of the endometriosis together with the degree of intestinal obstruction present. Decision to do a conservative operation implies that the surgeon must be sure that the intestinal lesion is *not* in fact a carcinoma † Because the treatment of intestinal obstruction varies with the location of the lesion the therapy of colonic obstruction will be discussed first followed by that of ileal obstruction.

a. Treatment when the point of obstruction is in the sigmoid, recto-sigmoid junction or rectum.—In these cases the involvement of the pelvis and colon by endometriosis is usually extensive and bilateral oophorectomy or panhysterectomy is usually indicated. Panhysterectomy is justified because the endometrioma of the colon will regress, the obstruction will be relieved and associated pelvic lesions, which are nearly always present, will be removed. If the obstruction is complete or incomplete with much dilatation of the proximal portion of the bowel, temporary proximal colostomy should also be done to decompress the bowel. The stoma may be closed in a few months after subsidence of the endometrioma. If the patient is a young woman who is desirous of a pregnancy and whose pelvic organs are essentially normal, resection of the involved segment of the bowel is the procedure of choice.

b. Treatment when the point of obstruction is in the ileum.—In these cases the treatment of choice is resection of the bowel; or, if the diagnosis is apparent to the surgeon, a short-circuiting procedure. The obstruction in these cases is to some degree caused by the partial occlusion of the lumen

* Radiation castration could not be expected to produce rapid regression of the obstructing intestinal lesion. Surgical castration alone on the other hand is often followed promptly by a "relenting" of serious obstructive symptoms.

† Chiefly among cases found early in our series, the surgeon felt reasonably certain that the intestinal lesion was malignant.

by the endometrioma but more by the tough dense adhesions of endometriosis and resultant kinking of the bowel.

2. *Surgical Treatment versus Roentgen Therapy*.—Roentgen therapy should be reserved for those patients who are extremely poor operative risks or who have had intestinal recurrence of endometriosis following operations in which conservative treatment was given to the ovaries.

Presumable Relationship of Endometriosis to Carcinoma.—The question whether carcinoma may develop from endometriosis or on the basis of it has been much debated. It is our conclusion that a presumable relationship may exist but there is no definite factual proof of it.

SUMMARY AND CONCLUSIONS

1. An analytic study of clinical data on sixteen cases of intestinal obstruction caused by endometriosis from the current series has been presented as well as the results of a pathologic study of these cases.

2. To make the diagnosis of endometriosis as a cause of intestinal obstruction, the possibility of its occurrence should be kept in mind in every case of intestinal obstruction in which the patient is a woman from thirty to fifty years of age. Acquired dysmenorrhea, menstrual periodicity of symptoms, sterility, rectal or pelvic pain, absence of loss of weight, the presence of associated uterine fibroids or ovarian cysts and a long history of intestinal symptoms which suggest progressive intestinal obstruction with frequent exacerbations at menstruation are most important points in the diagnosis of this condition.

3. Severe constipation, lower abdominal pain and distention are almost always present. If the obstruction is ileal, vomiting is almost always present, while if the obstruction is colonic, obstipation is more often present. Diarrhea is occasionally a symptom but the presence of gross blood in the stool in the absence of other anorectal disorders is very infrequent. If present at the time of menstruation it is of significance.

4. The symptoms of menorrhagia and metrorrhagia are not the symptoms of endometriosis per se but rather the symptoms of associated pelvic pathologic lesions.

5. An accurate preoperative diagnosis of intestinal obstruction caused by endometriosis can usually be made on the basis of the clinical history, digital examination, sigmoidoscopic examination and careful interpretation of the roentgenogram of the colon and the terminal portion of the ileum. The finding of a firm tumor in the rectovaginal septum or of tender palpable nodules plus the palpation of uterine fibroids and bilateral ovarian cysts is suggestive of endometriosis as the cause when intestinal obstruction is present. Sigmoidoscopic examination, with the presence of an extrarectal mass and an intact puckered mucosa, and a roentgenogram of the colon, with the presence of a long, inconstant filling defect with sharp regular borders and an intact mucosa, are the two most valuable adjuncts to diagnosis when the lesion is in the lower bowel.

6. *Surgical biopsy of tissue from the vaginal vault*, if the endometrioma is in the rectovaginal septum and has invaded the vaginal mucosa, may afford pathologic confirmation of the clinical diagnosis but biopsy of the rectal mucosa is usually noninformative, as the tissue in all the cases in which this was done in the current series was reported as inflammatory.

7. Obstruction of the ileum as caused by endometriosis presents a less characteristic clinical picture than that in the sigmoid or below.

8. The treatment of intestinal obstruction caused by endometriosis is surgical. A preoperative diagnosis of endometriosis as a cause of colonic obstruction will obviate the necessity for resection of the bowel in most instances and surgical treatment will consist usually of bilateral oophorectomy or of panhysterectomy with or without temporary colostomy as is deemed necessary. The procedure of choice in obstruction of the ileum caused by endometriosis is ileal resection with or without preliminary enterostomy and with or without panhysterectomy as indicated by the presence and degree of associated pelvic pathologic lesions.

9. The mechanism of ileal obstruction was usually due to kinking caused by the endometriosis, while the obstruction in the sigmoid and below was more often due to an impingement of the endometrioma into the intestinal lumen.

10. If the patient is a young woman who has a discrete endometrioma of the ileum or sigmoid causing intestinal obstruction, if the pelvic organs are essentially normal to the extent that there appears to be a reasonable chance of an ensuing pregnancy and if the absence of menorrhagia or cystic endometrium has indicated evidence of fair ovarian function, a conservative operation should be done as regards the ovaries and a radical operation done as regards the obstructed bowel. Intestinal resection without oophorectomy is indicated.

11. Microscopically, endometrial glands and stroma were found in all layers of the intestinal wall. They seemed to be most diffusely dispersed in the muscular layers. The endometriomas of the sigmoid were of the discrete or deep type, while the endometriomas of the ileum were located closer to the serosa.

12. Gross blood had been present in the stools of only three of sixteen patients. The intestinal mucosa on gross inspection was intact in all cases but on microscopic examination it was invaded by endometriosis in two cases. In one of these cases microscopic ulceration had occurred.

13. Fibrosis around the endometrial glands and stroma was characteristic in all of the sections but a positive iron stain representative of hemosiderin was not characteristic. The muscle fibers in most instances seemed to run in the same long axis as that of the endometrial glands.

14. A plea is made for biopsy, frozen section and pathologic confirmation of the clinical diagnosis in all cases of endometrioma obstructing the bowel, as carcinoma can be positively excluded only by this method. The prognosis of patients who have had intestinal obstruction caused by endometriosis is excellent and the surgical mortality rate was nil in the current series.

THE IRRITABLE BOWEL SYNDROME*

PHILIP WALLING BROWN

One is frequently confronted—and often confounded—with the comment: “Doctor, I do hope you can do something for my colitis. I have been to so many doctors and no one has been able to help me.” These remarks usually are offered by a woman but may be made by a man and, parenthetically, one might add that he is often the more difficult to satisfy.

Two definite questions raised in such an introduction do afford an immediate basis for consideration. The first is, “What is meant by colitis?” and the second is, “What is the correct diagnosis?” The patient’s search for a “cure” implies one of two extremes—either that he has an obscure disease or a functional disturbance. We physicians condemn use of lax, vague, diagnostic terms and decry indiscriminate prescription of diets without being willing to accept that the responsibility for such practices rests on our own shoulders. And always an undercurrent of anxiety is present in our minds that this “pat” comment may not be the plea of a patient who has a functional disorder and that some underlying or coexistent disease may give rise to it.

First the term “irritable bowel syndrome” must be defined. In this discussion, concern is not primarily with the patient who complains of constipation but with those who suffer from diarrhea, either intermittent or chronic, abdominal soreness, gas pains, cramping and varying degrees of ill health and inefficiency. This condition occurs most unusually in patients less than twenty years of age; it is a phenomenon which appears as life becomes more complex.

Often we physicians are tempted to minimize repetition of various studies that have been carried out previously but we should be reluctant to assume responsibility for management of this or any other condition without as complete knowledge as is possible. We must first convince ourselves that the diagnosis is correct in order to have any success in convincing the patient.

After the history has been taken and physical examination completed, the orderly sequence of studies of the intestine is conducted. Examinations of the stool for parasites and ova are essential, although in the North Temperate Zone the only clinically important parasite is *Endamoeba histolytica*. It is difficult for some of us to be sure that *Giardia lamblia* is a pathogen, while other flagellates as *Trichomonas hominis* and *Chilomastix mesnili*, along with all amebae except *Endamoeba histolytica* are definitely in the nonpathogenic category. *Ascaris lumbricoides* and hookworm ova may be encountered occasionally if the patient lives in an area where sanitation is poor. Symptoms due to tapeworms in the intestinal tract are nil.

Next is the study of mucosa of the terminal part of the large intestine, as seen through the proctoscope. If this procedure, together with studies made after a barium enema has been given, reveals nothing, not only the various types of true colitis but the presence of any form of tumor will be excluded from the diagnosis. Likewise, we know that approximately 90 per cent of patients who have regional enteritis have evidence of disease in

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the terminal portion of the ileum. The roentgenologist's study of the colon and terminal portion of the ileum will settle doubt concerning the presence of regional enteritis. Knowledge that the blood count and sedimentation rate are normal is of some secondary value. In a few instances, roentgenologic examination must be made at frequent intervals after a barium meal but only in a relatively small number of cases is this prolonged study warranted.

Many patients have had an examination of the gastric acids and low acid values are ascribed as part of the explanation of the bowel symptoms. Such may indeed be true and it is a simple matter to prove this in three or four days. The patient is told to sip a glass of water containing 30 to 40 drops of dilute hydrochloric acid with each meal. Unless a definite improvement is noted, there is no need for him to take the acid. It is a pertinent observation that of 100 patients who have achlorhydria, only about 10 per cent will complain of diarrhea. And of these ten, only one will be benefited by taking dilute hydrochloric acid.

A few instances of intestinal dysfunction associated with diseases such as hyperthyroidism, primary anemia, sprue and diabetes are encountered, but a correct diagnosis of these conditions is usually not long in being attained.

If after these diagnostic points have been considered, we have reasonably well satisfied ourselves that the patient's symptoms are not due to or associated with some organic disease, the real problem becomes evident: to explain convincingly the patient's condition to him. A fundamental start is to assure him positively that true colitis, cancer and such conditions are not present. Certain terms for the condition now known to be present have long been employed as a convenient "out." The more commonly used and most reprehensible terms are "mucous colitis," "spastic colitis" and "simple or chronic colitis." We must school ourselves never to use the word "colitis" unless there is actual inflammation of the colon. To do otherwise invariably gives the patient the impression that while it may not be a bad type of colitis, it is colitis.

To analyze and discuss the problem further, we must learn the background of the patient, as well as the precipitating factors that preceded the bowel symptoms. From the center of social and economic crises radiate the problems of fear of disease, environment, irregular habits and abuse of laxatives. Undoubtedly fear and lack of security are the fundamental problems. Heredity and congenital faults are additional factors.

To this group of contributing factors allergy, the one biggest stumbling block, must be added. The other factors may take time and persistent patience but the importance of allergy is the hardest for the doctor to evaluate. In some cases the answer is obvious but in others, such as those in which wheat is the offender, the simpler methods are not helpful. If only satisfactory preparations of food fractions were available for use in skin tests the problem would be simplified. Such experience as I have had has led me to consider skin tests for food allergy as all but worthless. The principle is correct and some clever chemist eventually will prepare correct fractions for such tests but until that time, food allergy is a problem. Of course a fairly accurate method of answering the question of which food is the cause of bowel trouble is to have the patient go without food for forty-

eight hours, taking nothing at all but water, and then to eat the suspected food. This form of diagnosis may be a bit Spartan but will settle any question of food intolerance in all but very rare cases. I make it a practice to instruct patients whose complaints are suggestive of the irritable bowel syndrome to watch for possible food intolerance. If they suspect any substance, I suggest that they eat or drink a fairly generous amount at a time when the stomach is empty and see if there is trouble. The principle is similar to that of a food diary.

Another plan, the elimination diet, is of course indicated in a few instances but it is such a laborious, prolonged regimen that one is rarely justified in employing it.

Somewhat related to the problem of food intolerance is that of abdominal migraine—that curious explosion from either end of the gastro-intestinal tract—which may strike day or night. At times it has seemed that allergy may be a factor but in more instances it is merely the explosion of nervous tension, and when it occurs without associated headache, the correct diagnosis may not be too easy. It is patients who have this condition who are sometimes too quickly subjected to removal of a “poorly functioning gall-bladder” and who are told, “the appendix doesn’t show on x-ray” or “the womb is tipped and there is a cyst of the ovary.”

Aside from allergy and migraine, the purely emotional factors as they influence bowel dysfunction are always difficult to explain to the patient. We are chided for our brisk and cheerful, “Well, now, there is nothing wrong with you.” While this is true of these patients in a sense, perhaps it could be better stated, “Our studies are of great satisfaction and comfort in that no disease process has been found.” Then we should proceed to explain that such is 50 per cent of what must be known to solve the problem and the remaining 50 per cent must be worked out in terms of the patient in relation to himself and his environment. This is obviously an individual approach and no rule can be established. It is my opinion that the great majority of these patients are not candidates for psychoanalysis—most of them can be reached by a reasonable expenditure of the physician’s time and patience. The group in which the correct diagnosis is psychoneurosis with obsession or fixation features is in the domain of the psychiatrist and, by the same token, it is futile for most of us to struggle to change the opinion of the patient who “knows” that the bowel is diseased.

A very interesting and considerable group of patients are those whose symptoms followed a definite disease such as amebic colitis, bacillary dysentery and so-called intestinal flu. Such patients may have persisting spells of diarrhea and more or less abdominal unrest. In the past I have treated such patients who have had amebic or bacillary dysentery with repeated courses of arsenicals, oxyquinolines and sulfa drugs because of the uncertainty and doubt that the offending organism might still exist. Gradually I began to appreciate that these patients had an irritable bowel as an aftermath of an infection. Reassurance of the patient that such is the case, that it has been encountered in others, and that the less one “doctors” for it, the quicker it will subside has done much to relieve them. As yet we have no sound explanation of why symptoms should persist but they do. Many veterans are presenting themselves with complaints suggestive of this type of the irritable bowel syndrome. By all means, careful studies of the stools

and bowel must precede diagnosis but certainly one must not label the condition "chronic dysentery" or "colitis" unless their presence is actually proved.

Eventually the physician has to answer the questions of "Well, doctor, what about my diet and what medicines should I take?" Diet and vitamins! "We are hoist with our own petard." A patient without one or more diet lists or who does not take supplementary vitamins is almost unique.

First, as to what shall be eaten: To me it seems most important to stress the fundamental fact that what one puts in the stomach is a highly individual problem. All of us will deliberate and fuss about the fit and appearance of our clothes and yet a ready-made diet list is accepted promptly as holy and final. The patient must understand that it is most unlikely that a fixed list of foods which can be suggested will be suitable. He must have adequate food, curtail, more or less, the intake of fruits and vegetables, and make personal observations concerning true intolerance. If time and circumstances permit and the patient wishes to do so, it is possible to work out with him what is to be eaten and drunk and recommendations are based entirely on his reports. The quicker he is "put on his own" and ceases to feel that he must be tied to his doctor's apron strings, the more promptly will the solution be attained. Occasionally a patient is encountered who drinks a needless amount of water and curtailing that may help to decrease intestinal onrushes. We have so built up the fetish of diet, especially in conditions in which specific therapy is of no value, that the patient considers the diet of far more importance than we really intend. Let us use the word "food" in a broad sense and avoid the word "diet," at least in this problem.

The figures of the sale of vitamins have become astronomical, due again to our own wishful thinking in so many instances, and sales have been accelerated amazingly by the cheerful, convincing patter of the detail men, to say nothing of "blurbs" via the radio. None of us should need to be reminded that only a small fraction of our patients require supplementary vitamins. As vital as they are in some instances, almost on a par with insulin and liver extract, so few patients really need them. If the patient cannot tolerate citrus fruits, it is erring on the safe side to recommend that he take 100 mg. of ascorbic acid daily. Likewise, if all meats are poorly tolerated—a rare condition—then taking a supplement of B complex is wise. If for any reason the patient cannot drink milk, he should take a heaping teaspoonful of tribasic calcium phosphate each day. It should be dissolved in half a glass of hot water and this should be drunk after sufficiently cool; it must be taken when the stomach is empty to promote the maximal absorption of calcium.

After we have established the diagnosis of irritable bowel, it is a corollary that no medication can be of any direct value. It is often practical to suggest that the patient take small doses of some sedative; the cheapest and most effective, as a rule, being $\frac{1}{2}$ grain (0.032 gm.) tablets of phenobarbital. The drug is to be taken before meals and possibly at bedtime, but again, advise the patient to use it when he feels under stress. He must appreciate that it is given to decrease emotional stress and drive and is not a medicine for the bowel itself. There is no objection to the patient's taking any of the inert substances such as bismuth, kaolin, pectin preparations and the various

combinations of these produced by the ingenious manufacturers. However, again, be sure that the patient uses them solely on the basis of hoping to decrease fluidity and frequency of the bowel movements. Furthermore, advise him to take them or leave them, depending solely on their value in his case. In the main, such preparations are merely that much more material to be excreted.

My experience has thus far been disappointing in the use of antispasmodics. From belladonna on to various recent products, little seems to be gained by their use. Many products are combined with phenobarbital and I think that administration of phenobarbital alone accomplishes just as much.

It should not be necessary to conclude with the remark that colonic irrigations are not even to be considered. This form of treatment seems to be declining, as well it should.

SUMMARY AND CONCLUSIONS

The irritable bowel syndrome is a condition that frequently is encountered in patients more than twenty years old. It is characterized by diarrhea—either steady or intermittent—abdominal discomfort and pains, increasing concern over food and medication, and more or less general poor health. In some instances, it is an aftermath of acute infections, such as bacillary amebic dysentery and so-called intestinal flu. A careful investigation is essential to convince first, the physician and for him, in turn, to convince the patient, that no disease process is the cause or coexists as a contributing factor. The term "colitis" should never be used unless actual inflammation of the colon exists. The term "proper or suitable food" should be used instead of "diet." Other than judicious use of mild sedatives, no medication is of any particular value.

DIVERTICULOSIS AND DIVERTICULITIS OF THE COLON*

PHILIP WALLING BROWN

Sacs of the colon may be either exceedingly serious problems or they may be simply matters of anatomic interest. Many people have diverticula of the colon. The incidence varies with the age group examined. Morton reports an incidence of 15 per cent in 8,500 necropsies, while Kocour found 1.9 per cent in 7,000. At the Mayo Clinic the figure is 8.5 per cent for the patients examined roentgenologically and 5 per cent for the cases in which necropsy is performed. These figures must all be considered in terms of age, for we know that diverticula of the colon are rarely seen in persons under the age of thirty years, that 4 per cent are encountered in persons between the ages of thirty and forty, and that approximately 93 per cent occur in persons forty years of age or older.

Physicians are familiar with outpouchings all along the gastro-intestinal tract from throat to anus; these outpouchings appear more frequently as

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the lower part of the bowel is reached. Benson, Dixon and Waugh observed 122 instances, from 1909 to 1942, inclusive, of small intestinal diverticula, exclusive of duodenal and Meckel's diverticula. In various studies a 2 per cent incidence of Meckel's diverticulum has been noted. Any of these sacs may provoke serious trouble but aside from Meckel's, it is odd how few cases of active diverticulitis occur except in the colon and esophagus.

Diverticulitis of the colon usually means that this disease is in the sigmoid and perhaps the descending colon so that most reports are based on active disease in this segment of the bowel. Occasionally one encounters acute diverticulitis in the right portion of the colon. As the onset of acute diverticulitis in such instances is almost always severe and the symptoms point to an acute process in the right side of the abdomen, exploration is undertaken. Such cases are rarely recognized preoperatively. For this discussion I shall conform to the custom of considering diverticulitis as chiefly a disease of the sigmoid colon.

Uncomplicated diverticulum of the colon or diverticulosis constitutes the lesion in the vast majority of cases in which these sacs are found. In one study of diverticula Marcey and I observed that of 1,100 consecutive cases which occurred from 1919 to 1928, inclusive, 10 per cent of the patients underwent operation and 25 per cent were classified as having medical diverticulitis, which left 65 per cent who were merely possessors of diverticula.

In a recent surgical study of this disease Pemberton, Black and Maino found recorded, in a five year period from 1941 to 1945, inclusive, 6,000 instances of colonic diverticula; 2.4 per cent of these patients underwent operation, 13.1 per cent were classified as having medical diverticulitis and the balance, or nearly 85 per cent, were merely possessors of the sacs. Why should there be this difference in the two series of cases? The fact that a greater percentage of patients in the latter series were examined roentgenologically, as well as the fact that a more critical recording of all diverticula was made in the latter series, even though there was no evidence of active disease, explains much of this great difference. This brings out the fact that one cannot state definitely in what percentage of cases diverticulitis will develop or in what percentage operation will be required. The age group studied, the diagnostic criteria of the roentgenologist and the number of patients examined are factors which will affect tremendously the relative numbers of cases of diverticula of the colon in the three divisions referred to in the two series of cases already mentioned.

Why do approximately 10 per cent of persons over the age of forty years have diverticula? It must be that these lesions develop at or beyond this age since so few are encountered in earlier life. The theory that has seemed logical to me is that they are herniations of mucosa through defects in the bowel wall at either the site of perforating vessels or at any point in the wall. It is conjectural that other factors such as aging, pressure or weight may contribute. Possibly some congenital defect in the bowel musculature may be at fault. It is not uncommon to find two or more instances in a family and Schlotthauer has even reported the occurrence of diverticula in seven brothers, while the two sisters had no diverticula.

Since it is impossible to state that any certain number of patients with diverticula will suffer from diverticulitis nor, of the latter group, how many

will require operation, it means that one should consider three subdivisions of the problem: (1) diverticulitis controlled by medical measures, (2) diverticulitis which requires surgical intervention and (3) diverticulosis

DIVERTICULITIS CONTROLLED BY MEDICAL MEASURES

When one or more of the sacs become diseased the symptoms are usually those of pain in the lower or left lower part of the abdomen associated with constipation in about five sixths of the cases and with diarrhea in the remainder. Nausea and vomiting are less striking symptoms unless considerable obstruction and peritoneal reaction exist. There is mild to moderate fever and leukocytosis is present. In other words the common signs of an inflammatory process whose actual source is merely suggested by some bowel dysfunction and by the site of the pain are manifested. Bleeding from the bowel in this group or any other group of patients with diverticula of the colon must be attended by a very low threshold of suspicion. I am even reluctant to admit that gross bleeding is due to diverticulitis. This may not be wholly correct but it is certainly the safer attitude to adopt.

Sigmoidoscopy is not only of distinct supplementary aid from a negative viewpoint but does afford definite contributory diagnostic assistance. Jackman and Buie list the following five signs that are strongly suggestive of diverticulitis: (1) limited mobility of a segment of the bowel that is normally freely movable, (2) angulation of the upper part of the rectum due to inflammation, (3) reduced lumen and adherent mucosal folds, (4) sacculatation of the sigmoid and (5) actual visualization of the diverticula. Of 242 consecutive patients with diverticula of the colon which they examined, they found one or more of the foregoing signs in 66 per cent and in thirty-five instances in this group they saw the diverticula.

The barium enema is the most helpful aid in establishing the diagnosis. The findings are obvious in many instances but in others there may be more than reasonable doubt as to the diagnosis and a coexisting carcinoma may be suspected. While there is now only historical interest in any relationship between diverticulitis and cancer, yet the problem of making a simple differential diagnosis in some cases is far from being a simple one. Every physician has been confronted with this question and no one more so than the roentgenologist. It would be presumptive on my part to discuss the various points that the roentgenologist must consider, and often the final decision must depend on the evaluation of both clinical and roentgenologic data.

Treatment.—This is relatively simple. Since rest of an inflamed part is important for recovery, the patient must stay in bed until the infection has subsided. Actual physiologic rest is not accomplished but is the only way short of disconnecting the bowel. As a general rule the patient should remain in bed from two to three weeks. Next to rest is heat and the best method is diathermy, with the electric pad and hot packs as second and third choices. The latter are heavy, quickly become cool and are the least desirable. Occasionally a patient will get much more comfort and seem to do as well by using ice bags instead of heat.

Hot saline rectal irrigations are of doubtful value and usually seem to cause more commotion than comfort. One may use a small saline enema or a retention enema of oil when it is necessary to aid elimination. If the pa-

tient is not too ill and can safely ingest liquids, it is of value to give a sulfonamide drug, preferably one which is absorbed at a relatively low rate such as sulfasuxidine or sulfathaladine. A dose of 2 gm. every four hours is suggested. Rarely in patients who will respond to medical measures is it necessary to give parenterally such drugs as sulfadiazine or penicillin.

At the onset the degree of distress, the abdominal findings and the general status of the patient will determine whether to permit oral use of fluids or to tide the patient along for a day or more with intravenous injection of solutions. As a rule liquids can soon be taken orally and food gradually increased to a reasonably normal intake.

Rather early in the treatment I like to have the patient take daily a small dose of mineral oil, that is, not over an ounce and maybe less. Such treatment administered between 9:00 and 10:00 p.m. will certainly not interfere with absorption of fat-soluble vitamins and the small dose is less likely to leak. Other than medication to relieve pain or promote rest, additional treatment is seldom required.

What is the outlook for the patient whose initial attack has subsided? Marcey and I found that 137, or 63 per cent, of 218 patients were well; of these 137, 106 had been well for five or more years. Of the eighty-one patients, or 37 per cent, in whom the results were considered as unsatisfactory, sixty, or three fourths of this group, had carried on with relatively little disability due to diverticulitis. As will be apparent in the next section, our present attitude would certainly be to urge operation in probably a fourth to a half of the patients in this less satisfactory group.

Can it be stated how many patients with medical diverticulitis might expect to require surgical intervention? From the preceding data one might hazard the comment that twenty-one of the 218 patients, or 10 per cent, should have been operated on. I think it reasonable to tell the patient whose initial attack subsides that he has about four chances in ten of some further trouble and about one or two chances in ten that an operation may be required.

DIVERTICULITIS WHICH REQUIRES SURGICAL INTERVENTION

In patients with diverticulitis who will require operative intervention the onset of illness is more severe and intense than in nonsurgical patients. They are usually sicker at the onset, there is minimal abatement of distress and, even though the process may show some temporary response to treatment, active trouble continues, due usually to perforation into the bladder, through the abdominal wall or into neighboring structures. The picture is more than just that of pain, bowel dysfunction, fever and leukocytosis, for there is more tumefaction than in patients in the medical group, and other curious symptoms may be noted. Everything is more dramatic than in the patients in the medical group.

All this is the picture of complicated diverticulitis, as opposed to uncomplicated or medical diverticulitis. The greater severity of symptoms in patients of the surgical group usually implies perforation with resulting increase of local and systemic reaction. Pemberton and co-workers emphasize this characteristic of the more intensive onset of the disease. In their study of 389 cases of diverticulitis of the sigmoid, 12 per cent of the patients were operated on within one month and 31 per cent within six months after

onset. In their series, 42 per cent of patients had either fistulas from prior exploration or spontaneous fistulas into the bladder or through the abdominal wall. The voiding of gas (pneumaturia) is practically certain proof of a fistula into the bladder.

A curious reference of pain in some cases often occurs. I have seen instances of severe pain in the lower part of the abdomen with radiation down the front of the thigh. This proved to be due to perforation and extension into the psoas muscle. Perforation of a single or solitary diverticulum with no evidence of bowel involvement, as seen by roentgenologic study, is rare. Pain in the hip or toward the back, fever and leukocytosis with little or nothing else, may be all one has on which to base a diagnosis. I know of no way to be certain in such a case other than to know that such may occur. We are all aware of the frequent diagnostic confusion which arises in cases in women, when so often a pelvic mass is mistaken for disease of the adnexa. Particularly is this more likely to occur when there are minimal symptoms of bowel dysfunction.

TABULATION

INCIDENCE OF POSTOPERATIVE DEATHS OF PATIENTS WITH DIVERTICULITIS TREATED BEFORE AND AFTER THE SULFONAMIDES WERE AVAILABLE

Operation	Before sulfonamides		After sulfonamides	
	Cases	Deaths	Cases	Deaths
Colostomy	117	6 (5 per cent)	89	1 (1 per cent)
Colostomy, later exteriorization	22	3	41	0
Colostomy, later resection and anastomosis	24	4	20	1
Exteriorization.	76	13	38	1
Primary resection and anastomosis	18	2	10	0
Total resections	110	22 (15 per cent)	109	2 (2 per cent)

Treatment.—Formerly the risk of surgical intervention in those seriously infected and complicated cases was high. Since the advent of sulfonamide therapy there has been a striking decrease in the operative mortality. This has been reported by Pemberton and co-workers and for the following surgical data I am indebted to their report. In their group of 245 patients treated before sulfonamides were available the over-all operative mortality rate was 14.7 per cent, while in their group of 144 patients treated after sulfonamides were available the mortality rate was 4.2 per cent.

The question is frequently asked whether one should close a colic stoma without first removing the segment of the colon which is the site of the diverticulitis. Even though one delays six or more months with the hope that the reaction will subside, the chances for ultimate success are poor.

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In thirty-eight instances of closure of the colic stoma, there were two post-operative deaths and twenty-three of the surviving thirty-six patients had recurrence of the diverticulitis. Hence it would seem that once surgical intervention is undertaken, it should be with the likelihood that resection will be necessary. Likewise excision of a perforated diverticulum or of a fistulous tract was found to have but a fifty-fifty chance of success, which further emphasizes that resection is definitely the method of choice.

It has been demonstrated that surgical procedures can now be carried out with a relatively small risk (tabulation). Hence there should be much less reluctance to advise operation, not only in the more obvious cases but likewise in the 10 to 15 per cent of medical cases that we have previously discussed as those in which unsatisfactory medical results are obtained.

DIVERTICULOSIS

As previously noted, at least 65 per cent, and probably 85 per cent, of patients in whom diverticula are found merely have diverticulosis. It is obvious that the vast majority of patients simply have diverticulosis. Are they likely to suffer from diverticulitis? May the sacs be the explanation of some of the vague gastro-intestinal complaints? Do they explain diarrhea in those cases in which there is no other objective finding? Certainly to all three queries one may reply, "Yes, but most unlikely." In a group of 220 patients with diverticulosis who were subjected to follow-up study, only one was thought to have later suffered from diverticulitis, which occurred nine years after the condition had been diagnosed; this patient died after operation. In no others of this group was there evidence then or in the follow-up study which would warrant ascribing trouble to the diverticula. There is no intent totally to dismiss diverticulosis as a nonentity but these observations do impress one with the need for caution in attributing complaints to diverticula which happen to be discovered on proctoscopic or roentgenologic examination.

These patients should always be informed of the finding of the diverticula and that these sacs are relatively frequent in people over forty. Likewise it is proper to explain that symptoms of diverticulitis may develop, although the chances are very small that such will happen. They should be instructed that it is good judgment to observe two simple rules that may minimize diverticulitis; namely, "Don't eat cinders" and "Take a swallow of mineral oil at bedtime." People seem to remember "cinders" as a key word and it helps them to avoid nuts, popcorn, bran and big seeds.

CONCLUSIONS

1. It continues to be my opinion that fate or some curious factor is associated with diverticula of the colon. A few patients are seriously sick (surgical diverticulitis), more are mild to moderately distressed (medical diverticulitis), while the vast majority seem to escape with no trouble at all (diverticulosis).
2. Medical treatment of diverticulitis is effective in about 63 per cent of cases. It is fairly satisfactory in 27 per cent, while it is unsatisfactory in 10 per cent.
3. Since the advent of sulfonamide therapy, the surgical risk in cases of

diverticulitis has markedly decreased. Certainly there should be less reluctance to advise operation in all cases in which the condition is not readily controlled by medical measures.

COMPLICATIONS PECULIAR TO ULCERATIVE DISEASES OF THE COLON*

NEWTON D SMITH

The complications which occur in the presence of ulcerative diseases of the colon are diverse and serious enough to deserve study. In some of these diseases the complications may be anticipated after the ulcerative disease has been diagnosed and in other of the diseases the complications are instrumental in indicating and diagnosing the disease. The physician, surgeon and specialist should know of these diseases and the complications.

CHRONIC ULCERATIVE COLITIS

In chronic ulcerative colitis complications are more numerous than in the other ulcerative diseases of the colon. Jackman and I in a previous study observed several interesting anorectal complications. The records of 871 patients who had chronic ulcerative colitis were studied. Fistula in ano had developed in 8.4 per cent of this group of cases. Twelve of the 871 patients were incontinent as the result of fistulectomy performed elsewhere. In addition, twenty-seven of the total group had anal ulcers other than fissure and twenty-four suffered from typical fissures. More interesting, probably, is the fact that thirty-two of the patients had undergone hemorrhoidectomy and noted symptoms of chronic ulcerative colitis immediately after the operation. In the group studied twenty-one patients had undergone hemorrhoidectomy elsewhere after the symptoms of the colitis had been observed. The wounds in the latter group healed more slowly than is usual in spite of the fact that every care was exercised to keep the wounds clean and to provide those conditions which insure satisfactory healing.

The analytic study of this group seems to lead to some interesting and important conclusions which will be applicable to all of the ulcerative diseases of the intestines. First, proctoscopic examination is imperative prior to any anorectal surgery. Second, anorectal surgical wounds and injuries respond differently in the presence of ulcerative disease of the colon than they do when the colon is normal. Even the more common anorectal lesions deserve serious consideration and the usual therapy must be altered because of the ulcerative disease involving the colon.

It seems an inescapable conclusion that abrasions, thrombosis and abscesses should be treated conservatively in these cases. Local cleanliness, the application of heat and mild antiseptics are helpful. All incisions must be conservative and curative operation postponed until the ulcerative disease is improved, the lesions are entirely healed or the diseased portion of

* *Abridgment of paper published in full in the New York State Journal of Medicine. 47. 2304-2306 (Nov.) 1947.*

the colon is excised. There are exceptions to these suggestions. Radical intervention may be indicated in those cases in which the complication of the sort mentioned seems to add so much to the burden that the patient is carrying, that improvement fails to occur in spite of satisfactory treatment or in cases in which the complication causes serious untoward reaction.

Chronic ulcerative colitis is noted for a number of complications which may occur during the course of the disease. The most interesting and most frequent complication is the development of polyps. Malignancy occurs less frequently. Some polyps observed can be classified as pseudopolyps and others are true adenomas. The true polyps occur as solitary polyps and multiple polyposis. In the latter, except for the tubular appearance of the intestine, the polyps resemble the congenital type when studied proctoscopically or roentgenologically.

Polyps seem to result from the continued effort of the intestine to overcome the destruction that takes place. It would appear that there must be some relaxation of that control which causes the healing process to subside when tissue injured or removed has been repaired or replaced.

Malignancy is a serious complication of colitis. It is prone to occur after the ulcerative disease has been present for a comparatively long time. The simultaneous development of more than one malignant lesion in the colon in the presence of chronic ulcerative colitis is not unusual. It is also interesting that the lesions are often of a high grade of malignancy.

Stricture is another complication which occurs in chronic ulcerative colitis and it may occur at any site in that portion of the colon involved by colitis. The stricture is real in contrast to the other contraction of the colon so characteristic of the disease. The stricture may be ringlike or tubular. This lesion appears in those cases in which the disease is most severe. It seems easy to understand the occurrence of this lesion when the penetration of the inflammatory process into the submucosal and muscular layers of the intestinal wall is recalled. In cases in which ileostomy or colostomy is carried out stricture occurs almost invariably and is frequently extensive.

Perforation and extensive hemorrhage can be explained by the amount of destruction of tissue and the extensive inflammatory process. Likewise, it would seem easy to understand the occurrence of massive phlebitis because of the debility of some of the patients and the blood-borne bacteria common to the disease.

Lesions of the skin are not a rare complication during the course of chronic ulcerative colitis. The improvement or extension of the lesions of the skin varies with the similar changes in the course of the colitis. In some of the cases huge sloughing ulcers in the skin develop which resemble the lesions of pyoderma gangrenosum and in others erythema nodosum develops. Unfortunately, in some cases in which lesions of the skin develop, patients may also suffer from arthritis.

Uveitis is observed in some cases of chronic ulcerative colitis. In others arthritis develops.

REGIONAL OR SEGMENTAL COLITIS

In discussing chronic ulcerative colitis I talked of the complications as occurring during the progress of the disease after the colitis had been diagnosed or should have been diagnosed. Conversely, in regional or seg-

mental colitis, the complication is often observed first and it aids in diagnosis. The appearance of fistulas in the anal and perianal regions, between the abdominal viscera and the colon, between the colon and the abdominal wall or between different portions of the colon are common in this disease. These fistulas occur spontaneously or after abdominal operation. When there is no mechanical basis for the fistulas, the physician should think of regional colitis or ileitis, especially when the patient is a young adult. The patient may or may not complain of abdominal distress.

In this disease it is not unusual to observe in the anal region indolent ulcers which occur spontaneously or after fistulectomy. Local treatment may be varied at will in the effort to assist in the healing of the ulcers but the result will prove the effort to be useless. Healing will progress at a remarkable rate when the disease is recognized and the damaged portion of the colon removed.

Penner and Crohn called attention to the tendency toward fistula formation in this disease and Jackman and I have discussed their observations also.

In the portion of the colon within reach of the proctoscope ulcers are sometimes observed in this type of colitis. These ulcers are usually shallow and irregular and are characterized by a tendency to bleed rather profusely following slight trauma. The remainder of the colon may appear normal. The ulcers in the colon also tend to disappear promptly when the primary lesion is removed.

Perforation or stricture at the site of the regional colitis occurs in some cases. Occasionally arthritis develops.

AMEBIC COLITIS

Amebiasis is noted because of the tendency for abscesses to occur in organs remote from the colon itself. Most common and well known is the hepatic abscess but similar lesions occur in the lungs, brain and urogenital organs. Abscesses and ulcers also occur in the skin, especially in the perianal region. Rarely, amebae have caused pericarditis.

In the presence of an epidemic of amebiasis it is advisable to study every lesion in the intestine for the presence of amebae. Lesions closely resembling carcinoma have been observed. A specimen should be removed and if amebae are discovered a course of antiamebic therapy should be administered.

Tuberculous ulceration or colitis will rarely cause perforation and in the hyperplastic type stricture may be produced. Most fistulas in *amo* will be infected with the tubercle bacillus if there is any tubercular colitis.

VENEREAL LYMPHOGRANULOMA

Venereal lymphogranuloma will often produce persistent proctitis and also stricture. While this is not typically an ulcerative disease of the colon it seems to belong in this group for study.

The changes caused by this disease and observed in the rectum, anus, perianal region, perineum and labia result from the involvement of the lymphatics. The resulting lymphangitis is accompanied by the formation of excessive fibrous tissue which forms the stricture, accounts for the

edema, the perianal tags and the peculiar sinus, as well as the elephantiasis of the vulva of some women who have this disease. The stricture observed in the rectum may be ringlike or tubular. It may develop promptly and extend rapidly or it may proceed slowly. The lesions observed may be true fistulas or only sinusses extending into the perianal tissue.

FACTITIAL PROCTITIS

Factitial proctitis which results from the application of radium to the cervix may be only superficial telangiectasia or a true ulcer. In the latter case contraction of the lumen of the rectum may occur or in some instances perforation through the base of the ulcer will cause a rectovaginal fistula. The ulcer is chronic and may persist for years.

THE SURGICAL TREATMENT OF CARCINOMA OF THE RIGHT PART OF THE COLON*

CHARLES W. MAYO

It is possible that the public gradually is becoming alert to the various manifestations of malignant disease, and therefore, in the presence of symptoms, is seeking the aid of the physician earlier than in previous years, but such is not known definitely to be true. It is heartening, nonetheless, to observe that between 1907 and 1938, inclusive, the resectability rate of malignant lesions of the colon in one large series which I studied was 67 per cent; whereas in another series between 1910 and 1916, inclusive, which I studied, the resectability rate was increased to 77 per cent.

A number of factors are responsible for the general improvement thus implied. The physician, for one thing, is becoming more and more impressed with the necessity for suspicion and investigation of the colon when a patient complains of fatigability and weakness and when anemia is found to be present. For another thing, the physician is now quick to realize that any digestive disturbance which is persistent and is associated with an alteration in intestinal habit calls for roentgenologic study of the colon.

It is still true, however, that earlier diagnosis is of paramount importance in the successful surgical treatment of malignant processes of the right portion of the colon. Improvement in the end results of such treatment is based on the fact that surgical intervention must be carried out before the malignant process has developed to such an extent as to limit the value of resection.

In the present paper I wish to present what I believe are significant data, gained from a recent review of cases, concerning malignant lesions of the right part of the colon. In addition, I shall describe a method of resection and of end-to-end ileotransverse colostomy, carried out in one stage, which has proved to be of considerable value.

* From *Minnesota Medicine* 30 1197-1201 (Nov.) 1917.

DEFINITION OF STRUCTURE CONCERNED

The term, "right portion of the colon," probably is ambiguous from the anatomic standpoint. Some writers have said that the abdominal portion of the colon is composed of two main parts, the right and the left, which would imply that the line of demarcation is in the middle of the transverse colon. When statistical material pertaining to the colon is under consideration, it is important to know exactly what a speaker or writer means when he concerns himself with this structure. In the present paper, as in past considerations of the right portion of the colon, I shall include the cecum, ascending colon and hepatic flexure only.

DIAGNOSTIC AIDS AND DIFFERENTIAL POINTS

Despite the advances in diagnostic procedures of recent years, it is still uncommon, in the presence of early lesions, to discover definite signs or symptoms to direct the physician's attention to the right part of the colon. It is still true, unfortunately, that when the diagnosis is made early, it generally is done so accidentally. A majority of patients (some 67 per cent) will have experienced symptoms for six months to more than a year before a correct diagnosis is made.

Many malignant lesions in this portion of the colon ulcerate as they progress. Some have a large surface area, a fact which explains the oozing of blood and the development of secondary anemia so often encountered and too frequently mistakenly treated as primary anemia.

Another diagnosis sometimes made for patients who really have a malignant lesion of this part of the colon is "acute" or "subacute appendicitis." In one study it became apparent that 15 per cent of the patients concerned had undergone appendectomy within the period in which symptoms caused by the malignant lesion had been present. This actually is an important consideration. When it is linked to the fact that only about 2 per cent of carcinomas of the right part of the colon develop among persons less than thirty years old, then it becomes clear that any incision for appendectomy should be adequate to permit surgical exploration of the right part of the colon.

Clear-cut symptoms of obstruction are not prominent. A marked degree of obstruction is rare because of the fluid nature of the intestinal contents on the right side and because constricting or napkin-ring lesions are unusual in this portion of the colon. Even so, a mass can be palpated in about 75 per cent of the cases.

If the lesion is to be detected before surgical operation, roentgenologic examination is essential. It should be done by one who understands roentgenoscopy. Double contrast roentgenography should be employed; in such a procedure the second roentgenogram is made with the colon inflated with air, after the harium has been expelled. Once it has been demonstrated that a malignant lesion is present, the situation becomes an emergency. Hence, no time should be lost in preparing the patient for surgical intervention unless operation is otherwise contraindicated. Time is of prime importance in the treatment of all malignant processes.

In view of present-day knowledge, the problem of diagnosis might be summarized by the statement that if digestive disturbances have been present, or a change in intestinal habit has persisted, in a patient who is

more than thirty years old, and if the stomach, duodenum and gallbladder have been ruled out as seats of the disturbance, then investigation of the right part of the colon certainly is indicated.

PREPARATION OF THE PATIENT

The preparation of most patients for operations on the colon requires about four days. Secondary anemia, if it is present, may have to be corrected. The group to which the patient's blood belongs and the Rh factor should be determined, because blood should be transfused in all cases, during or immediately after operation, when resection is performed.

As a rule, one of the sulfonamide drugs is employed in the preparation of the colon for operation. I consider sulfathaladine to be the drug of choice at present for the preparation of patients for resection of the right portion of the colon. This drug is administered by mouth in a dose of 1.5 gm. every four hours, until the patient has received 36 gm. Paregoric should be administered in doses of 8 c.c. at 2, 6 and 10 o'clock of the afternoon and evening before operation, in order to put the bowel at rest.

SURGICAL PROCEDURES IN GENERAL

It is a commonplace observation, but one which is still true, that the anesthetic agent of choice is the one with which the anesthetist is most familiar.

Surgical Technics.—Resection of the right portion of the colon can be carried out by a number of methods; any one of the methods encompasses still more differences of detail in performance. Again, every surgeon entertains certain preferences or antipathies toward various types of technic, suture material and suturing procedures, and surgical instruments. Hence, I believe it will be useful for me to consider the surgical trends, and to present only one surgical procedure which has been of value to me; namely, primary resection and end-to-end ileotransverse colostomy.

A number of years ago a colleague and I reviewed all the cases in which resection of the right portion of the colon for malignant lesions had been performed at the Mayo Clinic from 1907 to 1938, inclusive. The series comprised 883 cases I have just completed, with the assistance of the Division of Biometry and Medical Statistics, another review of cases in which resection was performed at the clinic from 1940 through 1946. Results of the latter study indicate that the following changes have evolved.

First, as I mentioned earlier herein, the resectability rate has increased from 67 to 77 per cent, so far as the Mayo Clinic series are concerned.

Second, primary resection and ileotransverse colostomy carried out in one stage have superseded two-stage and multiple-stage operations. In the past six years, 73 per cent of operations for the condition in question have been one-stage procedures.

Third, in 38 per cent of the one-stage operations, the particular procedures used have been primary resection and end-to-end ileotransverse colostomy.

Fourth, in 1946, resection of the right portion of the colon was carried out for malignant lesions in ninety cases, with no deaths in the hospital. In only three of these ninety cases was the operation done in two stages, and extraperitoneal resection was not performed.

Fifth, although a comparison of mortality rates between the period from 1907 to 1938 and the period from 1949 to 1946 is not a fair one, it is interpolated herein merely to emphasize the progress that has been made. From 1907 to 1938 the mortality rate associated with one-stage procedures was 22 per cent; for two-stage procedures it was 20 per cent. From 1949 to 1946 one-stage procedures were performed with a mortality rate of 3 per cent, and two-stage procedures were carried out with a mortality rate of 6 per cent.

PRIMARY RESECTION AND END-TO-END ILEOTRANSVERSE COLOSTOMY

To the time of this report, on my surgical service, one-stage resection and end-to-end ileotransverse colostomy have been accomplished fifty-four times, with one death. The two procedures at present constitute my operation of choice for malignant lesions of the right part of the colon.

I make a longitudinal incision at the outer border of the right rectus abdominis muscle through the rectus sheath. The rectus abdominis muscle is retracted medially and the posterior fascia and the peritoneum are incised.

After exploration for metastasis or other complicating factors has been completed, the right portion of the colon, beginning with the cecum, is mobilized. A wide segment of the mesentery of the colon is resected and the vessels are ligated deep.

The points for transection of the transverse colon and the ileum are selected with special consideration of the blood supply and the distance of these points from the lesion. I transect the ileum at an angle in order to insure a good blood supply to the cut edge and an adequate lumen to fit the colon. I have not yet encountered a case in which the ileum, cut in this manner, could not be made to fit the transected end of the transverse colon. I cut the colon and the ileum with the cold scalpel. I do not use the cautery because I believe that the heat involved devitalizes the tissue.

I do not, moreover, employ crushing clamps at the site of anastomosis. I establish an open type of anastomosis in which rubber-covered clamps are utilized to minimize soiling. Whatever questionable loss may be caused by some degree of soiling is more than compensated for by the accuracy with which sutures can be placed when the open method of anastomosis is used.

An outer row of running cotton suture is placed half way around the serosa. The mucosa is closed with a running catgut suture. The remaining half of the serosal coat is closed with interrupted cotton sutures. Only two rows of suture material are used because it is felt that more would interfere unnecessarily with healing.

The mesentery of the ileum and the mesentery of the transverse colon are brought together and closed in order to keep the small bowel from slipping through this opening. The raw surface on the right from which the colon has been removed is peritonized after retroperitoneal drainage has been established by placing two Penrose drains in position and bringing them out through a small incision in the right flank. Next, the region of the anastomosis is thoroughly swabbed with an antiseptic agent (phemerol); before the incision is closed 5 gm. of sulfonamide powder is sprinkled on the area intraperitoneally.

It is advisable, after the abdominal incision has been closed and before

the patient has recovered consciousness, to dilate the anus manually enough to paralyze the sphincters temporarily, so that gas cannot be retained. This procedure, I feel, is a very important part of the operation.

Except in one or two instances, it has not been necessary to employ a Miller-Abbott tube preoperatively. Thus far I have not found it necessary to use this tube postoperatively for any of the patients on my service.

Patients are permitted to walk early. Most of them are dismissed from the hospital in less than two weeks.

OUTLOOK FOR THE PATIENT

What the outcome will be for the patient operated on for malignant lesions of the right portion of the colon is an interesting problem in itself. The surgeon's objective is, of course, to maintain a good result over the years after operation, so that the patient will be assured of a happy and productive existence.

A number of factors determine the outcome after the operation in question. The pathologic grade of the lesion, the mural penetration of the malignant cells, the extent of metastasis to adjacent and distant points, and, of course, the age of the individual patient, all are important factors.

Some definite data are at hand, however. That is, if the patients in the present series are divided into two groups—those who did not have nodal involvement and those who did have nodal involvement, regardless of other factors—the certain five year survival rates appear to be valid. Sixty-four per cent of those patients who did not have involvement of lymph nodes lived five years or longer; 47 per cent of those who did have such involvement lived five years or longer. A recent study of malignant lesions of the rectum for which one-stage combined abdominoperineal resection was performed revealed that when involvement of lymph nodes was not present, 74 per cent of the patients lived five years or longer; but that when involvement of lymph nodes was present, 38 per cent of the patients lived five years or longer.

CONCLUSIONS

One-stage resection of the right portion of the colon can be performed with a lower mortality rate and lower morbidity rate than can multiple-stage procedures.

With certain rare exceptions, one-stage resection can be carried out in any case in which it is possible to do a multiple-stage procedure.

One-stage resection of the right portion of the colon, with end-to-end ileotransverse colostomy, constitutes an operation that has given very valuable results.

RESECTION AND PRIMARY ANASTOMOSIS FOR LESIONS OF THE LEFT PORTION OF THE COLON*

JOHN M. WAUGH AND MONTFORD D. CUSTER, JR

Primary aseptic anastomosis was performed in 107 consecutive cases (fifty previously reported and 117 additional cases) after resection of lesions of the left portion of the colon. Eleven patients died, giving a mortality rate of 5.6 per cent.

For lesions of the middle part of the sigmoid and above, this operation provides a safe, curative one-stage procedure, the hospital convalescence from which seldom exceeds three weeks.

For lesions of the lower part of the sigmoid, the rectosigmoid and the upper half of the rectum, this technic provides for the eradication of malignant lesions with preservation of the lower part of the rectum and the sphincter ani. The average period of convalescence in the hospital from this operation (anterior resection) is approximately one month.

The following conclusions are drawn:

1. Primary anastomosis is the procedure of choice after resection of lesions in the nonobstructed bowel.

2. Proximal colostomy is unnecessary for lesions of the middle part of the sigmoid or above, and is of questionable necessity or value for more distally situated lesions.

3. Palliative resection with immediate restoration of intestinal continuity is a logical and kindly approach despite a known increase of risk.

PROGRESS IN THE SURGICAL MANAGEMENT OF DIVERTICULITIS OF THE SIGMOID COLON†

JOHN DEJ. PEMBERTON, B. MARDEN BLACK, AND CHARLES R. MAINO

Since the turn of the century, when the clinical significance of diverticula of the colon first came into prominence through the writings of Graser, Fischer, Beer, Mayo, Wilson and Giffin, Moynihan, Telling and others, many valuable contributions to knowledge of the subject have been made by a host of workers. The literature is now voluminous, dealing with nearly every phase of the subject, such as the incidence, etiology and recognition of diverticulosis and the symptomology, classification, recognition and management of the secondary pathologic changes; that is, diverticulitis and its sequelae. Knowledge derived from these studies is widespread, so that the value of further discussion of the subject would appear to be limited to emphasis and appraisal of established facts were it not that in recent years surgery of the colon has made momentous progress. In view of these

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advances, re-evaluation of the surgical management of diverticulitis of the sigmoid seems definitely indicated to determine if the practice and teachings of former years are still valid.

Surgery in the management of diverticulitis is limited largely to the treatment of certain complications, notably perforation, obstruction and fistula. Brown wrote, "There should be a determined effort to avoid operation," but he pointed out that it was both futile and dangerous to persist in a medical regimen after development of the complications just mentioned. In addition to these classical indications for operation, it is frequently impossible to exclude carcinoma on clinical grounds, and exploration for this reason often is justified. There is lack of agreement as to what should be done surgically in the management of complicated diverticulitis, particularly as to the necessity of resection in many cases. Since the literature contains no report of a series of cases of diverticulitis in which surgical treatment has been carried out in conjunction with modern chemotherapy, the present study, therefore, was undertaken with a twofold purpose in mind: (1) to appraise the different surgical procedures in the management of diverticulitis of the sigmoid, and (2) to determine what effect the application of modern chemotherapy has had on the immediate mortality.

Records were available of 389 patients* whose diverticulitis involved the sigmoid only, or the sigmoid together with a portion of the descending colon, and who were treated surgically. For the purpose of this study, the patients were divided into two series; namely, series A, which comprised 215 patients treated surgically in the years 1908 to 1940 inclusive, and series B, which comprised 144 patients operated on in the years 1941 to 1945 inclusive. The data relating to incidence and symptomatology of the disease cited were derived from the records of the latter series (B), whereas the data relating to late results of treatment were obtained, primarily, from the earlier series (A). The surgical mortality rate of each series was computed.

It is estimated that in excess of 5 per cent of all individuals more than forty years of age have diverticulosis of the colon but the condition is rare among persons less than this age. Of more than 47,000 roentgenologic examinations of the colon made at the Mayn Clinic in the period 1941 to 1945 inclusive, diverticulosis was discovered in 8.5 per cent. It is not known in what proportion of patients with diverticulosis symptoms attributable to inflammatory changes in the diverticula will develop but Abell has estimated that 10 to 20 per cent, and Brown and Mareley that 12 to 16 per cent of patients with diverticulosis ultimately will have diverticulitis. In the same period (1941 to 1945, inclusive) the diagnosis of diverticulitis of the sigmoid was made in 600 cases, which represent 15 per cent of the cases of diverticulosis. Of the 600 cases of diverticulitis, in 144 cases, or 24 per cent, surgical treatment was employed. Thus, it can be estimated that in about one out of every four patients with diverticulitis complications requiring surgery will develop.

* Patients whose diverticulitis was discovered at operation directed primarily at treatment of some other lesion, and who were not treated surgically for the diverticulitis, were not included in this series. Five patients have been included two times in this series. In each case, the patients were treated surgically for diverticulitis, the disease recurred and another series of operations was carried out. There were actually 234 individuals in the series.

The age and sex distribution of patients in series B was in keeping with those of patients reported by others. The youngest male in the series was twenty-nine years, and the youngest female thirty-three years, of age; the eldest male was eighty years and the oldest female seventy-nine years of age, while the mean age was 53.6 years at the time of the operation. The ratio of males to females was 2:1.

Since diverticulitis may be severe from the onset of symptoms, it is not surprising that many patients required operation relatively soon after their first symptoms were noticed. In series B, 12 per cent of the patients were

TABLE 1

SYMPTOMS AND SIGNS OF DIVERTICULITIS OF SIGMOID IN 144 CASES
IN WHICH OPERATIONS WERE PERFORMED—SERIES B

Symptoms or signs	Cases	Per cent of 144*
Evidence of inflammation	114	79
Complete or partial intestinal obstruction	43	30
Diarrhea . . .	27	19
Mucus in feces . . .	9	6
Blood in stool	12	8
Fever	52	36
Abdominal	21	42
Pelvic	31	
Fistula	23	
Sigmoidal cutaneous	22	
Sigmoidovesical	4	
Sigmoido-enteric	7	
Multiple	5	
Other types		

* More than one symptom or sign encountered in each of many cases.

operated on within one month and 31 per cent within six months of the onset of the disease. It is of some interest that a greater proportion of patients in the older age groups were operated on sooner after the onset of symptoms than were the younger patients. Thus, of the patients in their forties or less, 19 per cent were operated on within six months of the first symptoms; of those in their fifties, 29 per cent, and of those in their sixties or more, 38 per cent.

The symptoms which the patients in series B presented are shown in table 1. Such symptoms and signs as tenderness, fever and leukocytosis have been grouped under the broad heading of inflammation. Many pa-

tients presented several of the symptoms listed. On physical examination, 36 per cent had a mass which could be palpated beneath the abdominal wall or through the rectum and 42 per cent had a fistula which had followed former operative procedures or had developed spontaneously. Certain other signs, not covered in table 1, were significant and will be set forth here. Evidence revealed by sigmoidoscopic examination was of considerable value in the diagnosis. Of the ninety-four patients who were subjected to sigmoidoscopy, findings suggestive of diverticulitis, such as unusual saccululation, angulation, fixation of the bowel, constriction of the lumen, edema of the mucous membrane or the presence of an extraluminal mass were recorded concerning 63 per cent, while one or more diverticula were visualized in examination of 14 per cent. Roentgenologic examination after bariun enema was of the greatest aid in the diagnosis. This procedure was carried out on 104 patients. The diagnosis of diverticulitis, diverticulosis or both was made in 66 per cent of this group, the diagnosis of an obstructing lesion was made in 22 per cent, the diagnosis of an obstructing lesion of questionable malignant nature was made in 3 per cent, and the diagnosis of a fistula of the sigmoid only was made in 8 per cent. Thus, in only 1 per cent did the roentgenologic examination fail to show any evidence of a lesion suggestive of diverticulitis or diverticulosis.

It is agreed generally that carcinoma is no more likely to develop in a segment of bowel involved by diverticulitis or diverticulosis than it is in a segment of bowel not so involved. Furthermore, the association of diverticulitis and carcinoma is not common. Rankin and Brown reported that in 227 cases of diverticulitis, carcinoma was encountered in only four and that diverticulitis was present in only four of 670 cases of carcinoma. During the period 1941 to 1945 inclusive, eleven of the patients who were successfully operated on for carcinoma of the colon or rectum were found, by the surgeon or pathologist, to be suffering also from diverticulitis of the sigmoid. In five cases the carcinoma was situated in a segment of bowel distant from the diverticulitis. Since the operative procedure was primarily directed toward removal of the carcinoma in all of the cases, the inflammatory lesion was considered of secondary significance and this group of eleven cases was not included in the series of cases of diverticulitis.

While there is perhaps no causal relationship between diverticulitis and carcinoma, the clinical manifestations and gross appearance at operation of these two stenosing lesions are frequently indistinguishable one from the other, as was first pointed out by Moynihan in 1907. In roughly 25 per cent of the cases in this series, carcinoma could not be excluded by clinical methods of examination. Even at operation the surgeon was unable to differentiate between carcinoma and diverticulitis in many cases. The error was made both ways and several cases of what was mistakenly considered to be locally inoperable carcinoma were proved subsequently to be cases of stenosing diverticulitis. More frequently, extensive resection was done to remove radically a supposedly malignant lesion, either without preliminary colostomy or within a few weeks after the establishment of a colonic stoma. It was thought that, for the patient's sake, sufficient time could not be allowed to elapse for the inflammatory reaction to subside. If the delay had been thought advisable, the inflammatory character of the lesion would have become evident.

SURGICAL TREATMENT OF DIVERTICULITIS

Various surgical procedures were employed to treat the patients in both series. The factors that influenced the choice of procedure employed were diverse, the most important of which were the presence or absence of obstruction, the acuteness of the process, the extent of the peridiverticulitis and of inflammation of the mesocolon, the presence or absence of fistula and the relative accessibility of the involved segment of the sigmoid. Patients treated surgically in essentially the same manner were grouped together and an attempt was made to evaluate the results following the different methods of surgical treatment, both as to the immediate mortality and the ultimate outcome. It is evident that when the involved segment of bowel is not resected, recurrence of the diverticulitis always remains a possibility.

The various surgical procedures to be discussed subsequently were all carried out at the clinic. Many patients in both series had had previous operations, because of diverticulitis, before they were first seen here. Since many such operations on patients in series A were of historic interest only, they will not be mentioned. The previous operations on patients in the more recent series B, however, reflect current practice in the more acute phases of complicated diverticulitis and have been summarized in table 2. The majority of these operations had obviously been emergency procedures, and in many cases the diagnosis had not been established before the operation. In about half of the cases an ileal, cecal or colonic stoma had been established, and in more than half of the cases drainage, coupled with appendectomy, colostomy or closure of a fistula, had been instituted. It is evident that the operations were of necessity limited by the extent of the inflammatory process, obstruction, or other factors in the great majority of cases. The results of the previous, usually limited operations, also are listed in table 2. Such limited operations, obviously, cannot be expected to cure the patient and, in cases in which drainage of abscesses that have resulted from perforated diverticulitis is instituted, the patients should be warned of the probability of fecal fistulas and that further surgical treatment probably will be necessary to effect a cure.

Local Excision of a Diverticulum or of a Fistula.—Rarely, the inflammatory reaction in a case of diverticulitis of the sigmoid is confined to a single diverticulum and the remainder of the colon is relatively unaffected, so that excision of the involved diverticulum and subsequent closure of the opening in the bowel may be considered. Similarly, either sigmoidovesical or sigmoidocutaneous fistulas occasionally may be so managed.

In series A, seventeen patients were treated in this fashion with one death in hospital, the result of a pulmonary embolism. Of the sixteen cases in which the patients survived operation, the results in two are not known; nine patients have remained well and five are not cured. Of the fourteen patients on whom the follow-up data were available, four had had sigmoidovesical fistulas and, of these, two fall in the group of nine who have remained well. Of the two others of this group of four, however, one has a persisting fecal fistula, and the sigmoidovesical fistula of one recurred; these two patients, then, fall in the group of five who were not cured. The other three of the five patients who were not cured have had recurring bouts of tenderness, fever and pain. In view of the limited inflammatory reaction which must have been present to permit satisfactory suture of the wall of

TABLE 2

DATA ON SURGICAL PROCEDURES PERFORMED IN THE CASES IN SERIES B
PRIOR TO ADMISSION TO CLINIC

Previous operations	Cases	Finding on admission	Cases
Ileostomy (2 months previously)	1	Ileostomy	1
Colostomy	12	Inadequate diversion	5
Drainage or removal of appendix	19	Abdominal fecal fistula	18
		Abdominal vesical fistula	1
Drainage, colostomy	4	Abdominal fecal fistula	2
		Abscess	1
		Cutaneous enterocolic fistula	1
Colostomy; closure	1	Cutaneous fistula	1
Drainage, attempt to close fistula	3	Cutaneous fistula	3
Colostomy, repair of sigmoidovesical fistula, closure of colonic stoma	1	Sigmoidovesical fistula	1
Cecostomy	1	Vesical fistula	1
Colostomy and repair of sigmoidovesical fistula	1	Sigmoidovesical fistula	1
Exteriorization operation	1	Persistent colostomy	1
Colostomy and resection of sigmoid	1	Persistent colostomy	1
Total	43		

the bowel, it would seem that the results following this procedure were unsatisfactory and unpredictable.

In series B, an attempt was made in three cases to excise a fistulous tract as a primary surgical procedure. Success was achieved in none. All three patients were ultimately cured by resection of the involved segment of sigmoid.

Colostomy.—There is general agreement that establishment of a stoma in an uninvolved segment of colon oral to that involved by the diverticulitis will be followed by marked subsidence of the inflammatory reaction. The procedure is advocated for relief of obstruction, for treatment of perforations into the free peritoneal cavity, and in many cases as a measure preliminary to resection of the involved segment of colon.

Of 245 cases in series A, a colonic stoma was established in 117. In the majority of cases, after the colonic stoma had been established, the involved segment was resected or the stoma was closed, but in thirty-two cases closure was not made. Two of these thirty-two patients died subsequently

of causes unrelated to their diverticulitis, and three other patients were lost track of. The remaining twenty-seven of the thirty-two patients were followed for sufficient time to allow evaluation to be made of the results following diversion of the fecal stream in the treatment of complicated diverticulitis. Two patients of the twenty-seven had sigmoidovesical fistulas and were not relieved entirely of their symptoms, while nineteen patients, including two others who had sigmoidovesical fistulas, considered themselves well. The remaining six of the twenty-seven patients continued to fail after establishment of the stoma and ultimately died, essentially of complications resulting from the diverticulitis. These six deaths would suggest that establishment of the stoma should not be postponed too long; in each case the death resulted from multiple pelvic abscesses and their complications, which probably could have been prevented had the fecal stream been diverted before the inflammatory process had become so extensive. In the usual case, however, establishment of the colonic stoma was followed by subsidence of most of the symptoms of the diverticulitis and, even when a sigmoidovesical fistula existed, considerable improvement occurred as long as the fecal stream was diverted completely.

Of the 144 cases in series B, colostomy was performed in eighty-nine, either as a stage preliminary to resection or excision of a fistulous tract, or as a definitive measure of treatment. Thus, a definitely greater proportion of patients in series B (62 per cent) were subjected to colostomy than in series A (48 per cent). However, of the eighty-nine patients of series B who underwent colostomy, only one died, a mortality rate of 1.1 per cent, compared with a mortality rate of 5.1 per cent in series A.

If a colonic stoma has been established, with adequate indication, for the treatment of diverticulitis, it would seem that there is no certain way to determine if the stoma can be closed without recurrence of the disease. Dixon stressed the time element and stated that closure should not be attempted for at least twelve months, while Jones expressed the belief that closure should not be attempted for from six to twelve months. W. J. Mayo wrote that closure could be done if the infective process had regressed spontaneously sufficiently to restore the lumen of the colon. Abell wrote that colostomy may permit such complete subsidence of the inflammatory process that the stoma can be closed; and Laufman, expressing much the same conception, wrote that if the infection did not completely subside after some months, then resection might be necessary. Judd and Phillips declared that not all patients who had colonic stomas would require resection, while Brown wrote that if a sigmoidovesical fistula was not present, the patient had about an equal chance that surgery beyond establishment of the colonic stoma would not be necessary. In our opinion, resection of the involved segment of the sigmoid should be advised in all cases before closure of the colonic stoma is attempted, unless the diverticulitis has subsided completely, as judged by clinical, proctoscopic and roentgenologic examination and, even in such cases, the patient cannot be assured of freedom from subsequent attacks of diverticulitis. We believe that this rather radical view is supported by the results in this series of cases.

In series A, thirty-one patients were treated by establishment of a colonic stoma orad to the diverticulum and the stoma later was closed. Closure was not attempted before six months had elapsed and, in one case,

it was postponed for sixty months. In two of the thirty-one cases, a sigmoidovesical fistula was closed in addition to establishment of the stoma. There was one death in hospital in the series following closure of a stoma which had been established before the patient came to the clinic. One case probably should be excluded from the series, since the diagnosis was not made with certainty before operation and since repeated roentgenograms of the colon after the stoma had been established gave negative results. Of the remaining twenty-nine patients, nine were well at the last report and twenty were known to have serious recurrent symptoms.

Of the nine patients known to be symptom-free, one has been followed one year or less, three for two years, one for three years, and four have been followed for more than six years since the stoma was closed. One patient in the group has remained well for seventeen years. Included in this group of symptom-free patients were two who had sigmoidovesical fistulas which were closed at the time that the stoma was established. It is evident that patients may remain free from symptoms of diverticulitis for prolonged periods without resection. However, in this series of cases, the satisfactory outcome was achieved with respect to less than one third of the patients who underwent closure without resection, and it would seem that it was impossible to predict with certainty before closure which patients would have symptoms subsequently.

Eleven of the twenty patients whose symptoms recurred had not undergone further surgery at the last report. The vesicosigmoidal fistula in two of the eleven cases had recurred, in one case after one year and in the other after eight years. Four of the eleven patients had persistent fecal fistulas associated with recurrent attacks of inflammation, and five patients suffered from recurrent attacks of inflammation and obstruction. The remaining nine patients had undergone further operative treatment at the time of the last report. A colonic stoma had been re-established in one case of the nine, a colonic stoma followed by resection of the involved sigmoid had been carried out in five cases and, in three cases, subsequent attempts to close the stoma had been made, all of which had failed.

Resection of the Involved Segment of Colon.—The majority of patients in both series were subjected to some type of resection of the involved sigmoid. It is our feeling that when adequate indications exist for surgical interference, the safest procedure is to establish, oral to the lesion, a colonic stoma that completely diverts the fecal stream and then to allow sufficient time for the inflammatory reaction in and around the walls of the sigmoid to subside before attempting further surgery. Whether or not subsidence has occurred can be judged from proctoscopic and roentgenologic examination but, as a rule, six months to one year should elapse before resection is undertaken. Obviously, whenever serious suspicion of malignancy exists, the resection must be undertaken much earlier. The presence of extensive peridiverticulitis materially increases the risk of resection. From the present review, it would seem, also, that exteriorization operations are safer than procedures in which primary anastomoses are attempted.

Preliminary Colonic Stoma; Subsequent Exteriorization Operation.—In series A, twenty-two patients were treated by means of a preliminary colonic stoma and a subsequent exteriorization operation. There were three hospital deaths in the group, a mortality rate of 14 per cent for the resec-

tion. Of the remaining nineteen patients, sixteen are well. Of the three remaining patients of the nineteen, one has continued to complain of pain in the region of the exteriorization operation and one committed suicide two years after the operation, presumably because of ill health. The final patient of the three died elsewhere of what was reported to be obstruction of the bowel one year after the resection.

In series B, forty-one patients had an exteriorization type of resection following establishment of a colonic stoma. There were no deaths in this group.

Preliminary Colonic Stoma with Subsequent End-to-end Anastomosis—In series A, twenty-four patients were treated by means of preliminary colonic stoma and subsequent resection with an end-to-end anastomosis. There were four deaths, a hospital mortality rate of 17 per cent for the resection. The colonic stomas of three patients who survived the operation were still open at the last report and one patient in the group has been lost track of. Fifteen of the sixteen remaining patients are well and one patient has a persisting fecal fistula at the site of the resection but no other symptoms.

In series B this type of operative procedure was performed on twenty patients with one fatality.

Resection without Preliminary Colonic Stoma.—There is a small group of cases of complicated diverticulitis in which it is relatively safe to perform a primary resection and to unite the bowel by end-to-end anastomosis. The criteria of safety for such a procedure are: 1. There should be no evidence of obstruction. 2. The inflammatory process should be chronic or mildly subacute. 3. The involved segment of the bowel should be short, so that after resection the two cut ends of the bowel which are to be united are free of inflammatory infiltration. Safety will be further assured if, before closing the abdomen, a temporary colonic stoma is established in a loop of bowel oral to the site of resection.

Primary resection of the involved segment of colon was carried out in ninety-eight cases in series A. An exteriorization type of operation was done in seventy-six cases, with thirteen deaths in the hospital. Primary resection with end-to-end anastomosis was employed to treat sixteen patients, with two deaths in hospital, and primary resection with side-to-side anastomosis was done in two cases without a fatality. In the four remaining cases, continuity of the bowel was not re-established and the patients were left with single-barreled colonic stomas. One of these patients died. The mortality rate of 16 per cent in these ninety-eight cases compares favorably with the mortality rate of the two-stage operation of preliminary colostomy and resection, which was 15 per cent. It is probable, however, that patients treated by primary resection had no obstruction and less extensive and less complicated diverticulitis than did those treated by means of preliminary colostomy and subsequent resection.

As mentioned above, primary resection without anastomosis was attempted in four cases; each of the patients was left with a single-barreled colonic stoma. The indication for this procedure usually was that the bowel was so shortened that neither an exteriorization operation nor primary anastomosis was thought feasible at the time of resection. One patient, as has been said, died following the operation, one patient subsequently under-

went successful anastomosis between the sigmoid and the rectosigmoid and two patients remained well but with the colonic stoma.

Now to cast back a few sentences to primary exteriorization operations. Results were comparable to those following other types of resection. Fifty of the sixty-three patients who survived the operation were entirely well and nine others were well but had fecal fistulas at the site of the exteriorization. In seven of these nine cases one attempt at closure failed and in two of the nine closure had not been attempted. Two patients of the fifty died of causes unrelated to their diverticulitis and two others complained of persisting pain in the region of the operative incision.

Fourteen patients survived the operation of primary resection with end-to-end anastomosis. Nine patients were well at the last report. Three had persisting fecal fistulas with attacks of inflammation. In one case of this group of three, a colonic stoma was made subsequently and since then the patient has remained well, with the stoma. In the remaining two cases of the fourteen, strictures of the bowel developed at the site of the anastomosis. The late results following this type of resection were less satisfactory than those following other types of resection.

In series B, primary resection of the involved segment of sigmoid was carried out in forty-eight cases. An exteriorization type of resection was performed in thirty-eight cases with one fatality. In six cases, primary resection of the sigmoid with end-to-end anastomosis was performed and, before closure of the abdomen, a temporary colonic stoma was established in a loop of bowel oral to the site of the resection. All the patients survived. Primary resection with end-to-end anastomosis without colostomy was carried out in four cases with one fatality.

Other Operative Procedures.—In series A, other procedures were carried out rarely, usually because of unusual circumstances. In two cases, after preliminary colostomy, the involved segment of colon was resected and the ends above and below the resected portion were turned in and dropped back into the abdomen. One of the two patients died of pulmonary embolism and the other remained well, with the double-barreled stoma. Cecostomy in two cases, ileostomy and appendicostomy in one case each, were carried out for treatment of high grade obstruction. Three of the four patients died and the remaining patient recovered and required no further surgical treatment. Ileocolostomy was attempted in three cases with one death in hospital. One patient had recurrent partial obstruction and one a persistent fecal fistula after this procedure. In two cases the sigmoid was simply wrapped in omentum. One of these two patients continued to have recurring attacks of diverticulitis, while the outcome in the other case is not known. In three cases, drainage of an abscess caused by diverticulitis was the only surgical procedure employed. The results in all three cases were poor. In one other case, the sigmoid was freed up and sutured to the body wall with no improvement in the symptoms.

Miscellaneous procedures which included resection, and which were employed in series B, are listed in table 3.

Mortality in Series A and B Compared.—The surgical procedures employed and the mortality rates in the two series are shown in table 4. In comparing the two series, the most noteworthy feature is the marked reduction in mortality rate in series B, to 12 per cent, together with a

decided rise in the rate of resectability. Of the 245 patients in series A, resection of the involved segment of sigmoid was carried out in 146, or 60 per cent, whereas of the 144 patients in series B the bowel was resected in

TABLE 3

MISCELLANEOUS SURGICAL PROCEDURES CARRIED OUT AT THE MATO CLINIC IN SOME OF THE CASES OF SERIES B

	Cases
Drainage of pelvic abscess	1
Closure of colonic stoma	6
Stoma established elsewhere	4
Stoma followed resection of sigmoid elsewhere	2
Colostomy and closure of jejuno-colic fistula	1
Colostomy and repair of fistula	2
Colostomy, repair of fistula and closure of colonic stoma	4
Colostomy, resection of sigmoid ileosigmoidostomy and partial colectomy	2

111, or 77 per cent. The contrast between the two series is even more striking when the mortality rate in the cases in which resection was performed is compared. Of the 146 patients (eight from the miscellaneous group of table 4) in series A who underwent resection, twenty-four died in

TABLE 4

SURGICAL PROCEDURES AND MORTALITY RATE

Surgical procedures	Series A 1908-1940			Series B 1941-1943		
	Patients	Deaths	Per cent	Patients	Deaths	Per cent
Colostomy only	33	6	13.8	12	1	8.3
Colostomy, subsequent closure	31	1	3.2	7	1	14.3
Colostomy, subsequent exteriorization	22	5	13.6	41	0	0
Primary exteriorization	76	13	17.1	39	1	2.6
Colostomy, subsequent resection and end-to-end union	24	4	16.7	20	1	5.0
Primary resection, end-to-end anastomosis and colostomy	0	0	0	6	0	0
Primary resection, end-to-end anastomosis. No colostomy	16	2	12.5	4	1	25.0
Miscellaneous	33	7	18.4	16	1	6.2
	245*	36	14.7	144	6	4.2

*As explained in the text (paragraph 3), there were actually five patients less than 245.

hospital, a mortality rate of 16 per cent, whereas of the 111 patients in series B who underwent resection, three died, a mortality rate of 2.7 per cent.

Of the six patients in series B who died, infection attributable to the operation was the cause of death in three cases. Infection of the abdominal wall developed in two cases following resection and in the third peritonitis developed two days following repair of a jejunocecal fistula that was caused by the crushing of the spur of a colostomy that had been performed elsewhere. The fourth patient of the six died of gangrenous cholecystitis following closure of a colonic stoma. The fifth patient, a woman, seventy-one years old, whose intestine was acutely obstructed, died from bronchopneumonia twenty-four hours after colostomy. The sixth patient died of cerebral hemorrhage fourteen days following an exteriorization operation and abdominal hysterectomy.

COMMENT

We are convinced that the improved results obtained in series B are definitely attributable to chemotherapy. Nevertheless, the two series of cases are not altogether comparable because, in the past twenty years, other changes in routine surgical management in all colonic cases may have influenced the results. A more accurate appraisal of the value of chemotherapy in surgery of the colon could be obtained by comparing the results of two large series of colonic cases in which conditions were practically identical except that chemotherapy was employed in one series.

Since the organization of a special colon service in the Clinic nearly twenty years ago, all patients with lesions of the colon and rectum who are considered candidates for major surgical treatment have received pre-operative treatment in the hospital for three to five days or longer, depending on the condition of the patient. The principal objectives of the treatment are: (1) to decompress and cleanse the large bowel; (2) to combat loss of blood and to establish and maintain protein balance by blood transfusions, (3) to combat dehydration by intravenous injection of saline and glucose solutions; (4) to establish and maintain concentration of vitamins, especially as regards vitamins C and K; (5) to combat potential infections by chemotherapy.

In the fall of 1939 we began using the sulfonamide compounds in colonic surgery. At first, perhaps because of the surgeon's innate skepticism concerning the value of drugs, especially any drug with such advance build-up as had been given to the sulfonamide compounds, 5 to 10 gm. of the crystals were only occasionally placed in the peritoneal cavity prior to closure of the wound in those cases in which peritonitis was feared because of actual or suspected soiling. As experience enlarged, the surgeon slowly, and perhaps with reluctance, became convinced of the efficacy of the sulfonamide compounds and began to use them routinely. Since 1942, following the research of Poth, succinyl sulfathiazole (sulfasuxidine) has been given by mouth routinely as a preparatory measure, 12 to 15 gm. daily over a period of three to five days. In recent years, after the supply of penicillin became readily available, this substance has been used frequently as an added measure of therapy. Other than the introduction of chemotherapy, there has been in the Clinic no major change in the management of colonic and rectal lesions during the past twelve years. Since, therefore, there was only one variable factor of importance in the management of patients during

this period, it appeared worth while to compare the immediate surgical results in cases in which the patients had not had the benefit of chemotherapy with those in which the patients had received it. For this purpose, the yearly hospital mortality rate of all patients who had undergone any

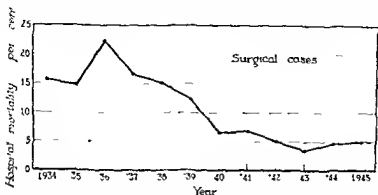


Fig. 29.—Mortality among patients subjected to operation for malignant lesions of the large intestine and rectum, 1934-1945

operation for carcinoma of the colon or rectum from 1934 to 1945 inclusive, was computed. As figure 29 reveals, the mortality rate before 1939 varied between 15 and 20 per cent. A slight drop occurred in 1939, the year in which the sulfonamide compounds were first casually or intermittently used, and then, in 1940, there was a precipitous drop to around 3 per cent, where the rate has since remained.

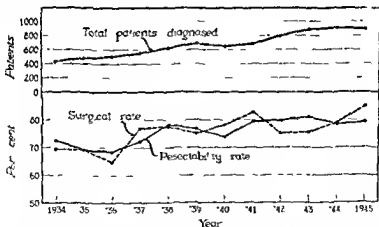


Fig. 30.—Resectability rate of patients with malignant lesions of large intestine and rectum, 1934-1945

In addition, the yearly surgical and resectability rates for the same twelve years were determined. The surgical rate is defined as the number of cases in which operation was performed divided by the total number of cases in which a diagnosis of carcinoma of the colon or rectum was made. The resectability rate is the number of patients on whom resection was

performed divided by the number of patients on whom operation was performed. As indicated in figure 30, there has not been a decline either in the surgical rate or in the rate of resectability during the years of decline in mortality; instead, there has been an appreciable rise.

Finally, in order to determine the influence of the factor of infection on the hospital mortality rate, the cause of death of all patients in this series was tabulated. Since peritonitis and pneumonia are unequivocally infections, it seemed pertinent to compare the incidence of these two complications as a cause of death in those cases in which the patient had received little or no sulfonamide compound with those in which the patient had received adequate dosage of sulfonamide. As indicated in figure 31, the mortality rate in each category decreased as the years passed.

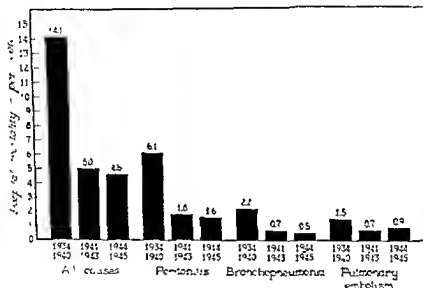


Fig 31—Causes of death. Mortality from various causes of death following operations for malignant lesions of the colon and rectum, 1934-1945.

The marked reduction in the hospital mortality rate associated with the surgical treatment of diverticulitis suggests that the indications for surgical treatment should probably be broadened. As indicated previously, there is general agreement that uncomplicated diverticulitis should be managed conservatively and that surgical treatment should be advised only if complications have developed. Nonsurgical treatment has definite limitations. It cannot be relied on to bring about complete subsidence of the inflammatory process, nor to prevent development of complications which will require operation, nor even to free the patient from his symptoms. It follows that in many cases under nonsurgical management, the patient has some disability and there is always the possibility of the subsequent development of complications which will require operation. Furthermore, as we have demonstrated, the safest type of operative treatment for complicated diverticulitis is the establishment of a colonic stoma orad to the inflammatory segment of bowel, followed by resection of the involved

segment after many months of the patient's living with his colonic stoma. Both the reluctance to advise surgical treatment and the choice of staged operations in the past is readily understandable in view of the former mortality rate of approximately 15 per cent. With a reduction of the mortality rate to about 4 per cent, the proposal that operations should be advised for less complicated diverticulitis may be seriously entertained. It is probable, as well, that the surgical mortality rate could be reduced even further if patients with less extensive disease were operated on, and certainly a greater number of single-stage procedures and even resections with primary anastomoses could be carried out safely. The advantage of removal of the involved segment of bowel, with subsequent cure of the patient, is evident when the uncertainty associated with nonsurgical management is considered.

SUMMARY

While the great majority of patients suffering from diverticulitis of the sigmoid portion of the colon respond satisfactorily to nonsurgical management, the complications of perforation, obstruction and fistula usually require operation. Surgical exploration, and frequently resection of the involved segment of colon, are indicated at times because of the impossibility of distinguishing with certainty between carcinoma and diverticulitis. In the present series, carcinoma could not be excluded with certainty in about 25 per cent of the cases in which a preoperative diagnosis was ventured.

Local excision of an inflamed diverticulum, or local excision of a fistula and closure of the wall of the bowel was possible rarely, but was followed by unsatisfactory results in approximately half of the cases in which it was attempted.

The establishment of a colonic stoma oral to the lesion was associated with a hospital mortality rate of 5.1 per cent in those cases in which treatment was given in the era before chemotherapy was available and with a rate of 1.1 per cent in those cases in which chemotherapy was employed. Excluding a small group of patients who died essentially of pelvic abscess and infection, a large percentage of the patients with a colonic stoma oral to the lesion remained clinically well as long as the stoma was maintained. Of the patients whose stomas were closed and resection of the bowel was not done, only about a third remained well. Results following closure of the stoma without previous resection of the involved segment of bowel were so unsatisfactory that we are of the opinion that, as a rule, resection should be done in all cases unless proof can be established of complete subsidence of the inflammatory process.

The safest plan of treatment proved to be establishment of a colonic stoma oral to the lesion followed, after an interval of six to twelve months, by an exteriorization type of resection. Resections of this type were associated with a hospital mortality rate of 13.6 per cent in the era before chemotherapy but there were no deaths after chemotherapy became available. The results after both primary resection and following resections done after establishment of a colonic stoma were satisfactory in that approximately 80 per cent of the patients were cured. The results were less satisfactory in the group of patients who underwent primary resection with end-to-end anastomosis of the bowel.

The employment of modern chemotherapy in the surgical management of complicated diverticulitis of the sigmoid has partially eliminated the occurrence of serious infections and thereby has been the major factor in the marked reduction of the surgical mortality rate from 14.7 per cent to 4.2 per cent.

With the risk of operation so markedly reduced and in view of the obvious advantage of resection, serious consideration can be given to broadening the indications for surgical treatment for diverticulitis.

CARCINOMA OF THE RECTUM AND RECTOSIGMOID*

CLAUDE F. DIXON

Some localized carcinomas of the rectum proper, in which the neoplastic disease does not involve more than the mucosa and submucosa, may be adequately treated by excision without prolonged interference with functional activity. In some instances it is necessary to divide the anal sphincter muscles completely in order to obtain satisfactory surgical exposure. It must be emphasized again and again that such local excision of malignant growths of the rectum can be carried out safely in only a small percentage of cases because most rectal carcinomas when first recognized are of size and extent that preclude local excision as an adequate operation. One may say therefore that by far the majority of rectal cancers require some type of radical surgical procedure.

Hochenegg in 1888 suggested and carried out the "pull through" operation for rectal cancer. In this procedure he freed the pelvic colon by means of an abdominal approach, then by a perineal approach he excised the diseased segment of rectum or the entire rectum and then pulled the healthy distal end of the sigmoid colon through the anal sphincter muscles. This appeared to be the answer to the problem of rectal cancer. There are, however, to my notion, two possible reasons why this procedure may meet with disapproval. First, the nerve supply of the internal sphincter may be severely interfered with, thus eliminating the involuntary control of the bowel. Second, such a procedure does not permit of radical excision of the perirectal tissue, which often is shown to be the site of secondary spread of the disease. Hochenegg's procedure, now employed by Babcock, Bacon and others, is apparently being rejuvenated. From my experience the "pull through" or Hochenegg operation for rectal cancer, like the local excision previously mentioned, has limited use; namely, only in small localized lesions.

More radical surgical removal of rectal carcinoma is brought about by the Miles combined abdominoperineal operation with a permanent single-barrel abdominal colonic stoma or by the so-called Kraske or Lockhart-Mummery operation in which a permanent loop type or double-barrel abdominal colonic stoma is established and is followed by a perineal resec-

* Abridgment of paper published in full in *Arizona Medicine*, 5: 41-45 (Mar.) 1948.

tion of the rectum. The latter usually is performed as a secondary procedure after the lapse of ten to fourteen days.

The combined abdominoperineal operation carried out in a single stage may fail to meet some of the requirements for which the procedure was designed. In the first place, most of the surgeons employing it emphasize the importance of radical excision in the abdominal portion of the operation and then during the perineal or final stage of the intervention they fail to carry out a radical excision of the perirectal tissues, which often are the site of direct extension or nodal spread of the disease. In the original essay on the procedure Miles stated that lateral spread of rectal cancer rarely if ever occurred. This view, as many of you know, has not been substantiated. True it is that the combined abdominoperineal procedure often effects permanent relief of rectal cancer. However, some patients for whom "cure" is expected return because of recurrence of the disease in the perineum. Such recurrences, at least in part, according to my observation and opinion, are due to malignant tissue or involved nodes which could have been removed in some instances had a more radical perineal dissection been carried out, for example, by wide excision of the perirectal fat, fascia propria and levator ani muscles.

It is important, I believe, to keep in mind that such radical, and I think necessarily radical, perineal operations are associated with considerable shock; therefore it is at present my custom to perform the Miles (combined abdominoperineal) operation in two stages. At the initial procedure the abdominal cavity is approached by means of a low rectus incision. The colon is divided between two Payr clamps at a site near the level of the sacral promontory. The sigmoidal mesentery, including the superior hemorrhoidal vessels, is divided and ligated. The posterior parietal peritoneum is incised only at the base of the mesentery where the superior hemorrhoidal vessels are clamped, divided and ligated. The left ureter also is identified and isolated. Next the proximal end of the distal sigmoid is inverted and the segment of bowel is dropped free into the pelvis. The small defect in the posterior parietal peritoneum is repaired by means of two or three interrupted catgut sutures. Finally, the distal end of the descending colon is brought through the primary incision or through a small muscle-splitting incision in the left iliac region, establishing a single-barrel stoma. In performing the colostomy the anterior peritoneum never is sutured to the bowel, which is held in place by means of a Payr clamp. The day following operation, the colon is opened by means of a cautery immediately beneath the clamp. The clamp automatically becomes detached on the fifth or sixth postoperative day. After a period of ten to fourteen days the colonic stoma is functioning satisfactorily. Such patients are out of bed on or about the fifth postoperative day.

The second and final or perineal operation is carried out with the patient under low spinal or sacral anesthesia produced by 100 to 120 mg. of procaine hydrochloride. The patient is placed in a reverse Trendelenburg position and the distal segment of bowel, which includes the rectum and sigmoid colon, is removed. An ounce (30 c.c.) of merthiolate is instilled through the anus. Swabbing of the anorectal tissues must not be done, since this maneuver might force some of the malignant cells from the rectal growth into the lymphatic or circulatory system. Furthermore cer-

tain types of bacteria which occur in the lesions secondarily may be dislodged into the same channels, producing such serious or fatal infectious processes as bacterioides, a complication that I have emphasized in previous publications. Next the anus is closed by means of a purse-string type of suture. Then with the cautery an incision is made beginning at the level of the base of the coccyx and extending about 3 inches (8 cm.) lateral to the anus downward to a midpoint in the perineum. Following this a similar incision is made on the opposite side. The coccyx is then disarticulated and removed and the fascia propria is incised in the coccygeal region. Now the perirectal fat, fascia and levator ani muscles are widely removed from both sides of the bowel. The rectum is next freed by cautery dissection from the prostate gland or posterior vaginal wall. In the male, caution must be taken during excision to avoid injury of the membranous urethra. After this the upper rectum is freed from the hollow of the sacrum by passing the left hand cephalad between the bowel and the sacrum until the inverted end of the sigmoid is reached. It is then grasped and drawn downward into the perineal wound, the lateral ligaments or rectal stalks are divided and the entire distal segment is removed. Five grams (75 grains) of microcrystalline sulfathiazole are placed in the peritoneal cavity. The perineum is closed transversely and the perineal wound is packed by means of first, a large square of synthetic silk, and secondly a 4 inch (10 cm.) gauze pack varying in length from 4 to 6 feet (122 to 183 cm.). The cutaneous edges are approximated about the pack with catgut sutures. The pack is removed on the third postoperative day. On the fifth or sixth postoperative day, daily sitz baths are begun.

Following this type of perineal resection the patient is kept in the hospital ten to fourteen days. Complete healing occurs in six to twelve weeks. This procedure I have carried out in about seventy-five cases without a death. The sacrifice of the superior hemorrhoidal vessels has in no instance caused necrosis of the distal segment of bowel. However some microscopic necrosis of the cancerous lesion does occur. I believe that this operation is radical in nature and I think that it has merit. Another possible advantage of this two-stage combined abdominoperineal procedure (combined with the one-stage operation) is that, according to my experience, it gives rise to less "shock" in patients sixty-five years of age or older and therefore there is lower morbidity and mortality.

Finally, in considering surgical procedures of the removal of rectal cancer, a safe and quite radical operation and one which I have found carries low risk is the Kraske operation, so-called. This consists in an abdominal loop or double-barrel colostomy followed in ten days or two weeks by perineal or posterior resection of the rectum and rectosigmoid. In this operation, as is well known, the abdominal cavity is entered and explored by means of a low left rectus incision. A loop of distal descending colon or sigmoid is brought out and fixed in the midportion of the incision. Fixation is accomplished by passing a rubber-covered glass tube through the mesentery of the bowel. The abdominal wall then is closed about the small loop or knuckle of the exteriorized colon. One should exercise great caution in establishing this type of colostomy in order not to close the abdominal wall too tightly around the bowel. If this error is made, marked edema of the exteriorized bowel will ensue, causing a poorly functioning

colonic stoma. Also, any slack or redundancy of the bowel proximal to the site of the colostomy will often permit the proximal segment of the bowel to prolapse, requiring amputation. The second and final stage of the operation is carried out as was previously discussed in describing the two-stage combined abdominoperineal operation, with one exception, and that is that in the Kraske type of operation with a loop colostomy, the peritoneum is opened during the rectal resection and the remaining distal end of the sigmoid is inverted and replaced in the peritoneal cavity and the posterior incision is packed as previously described.

CARCINOMA OF THE LOWER SIGMOID OR RECTOSIGMOID

In 1930 I became interested in the removal of carcinomatous lesions of the lower sigmoid by means of a procedure which would permit the re-establishment of continuity of the bowel. This idea occurred to me for the following reasons: I was impressed by the good results which had been obtained in the care of rectosigmoidal carcinoma by the Hartmann operation. This procedure is characterized by a one-stage resection in which the rectosigmoid or upper rectum is cut across a few centimeters distal to the growth. The upper rectum is then inverted and the remaining pelvic portion of the colon together with the growth is mobilized. Then the bowel is divided in the region of the distal descending colon. The proximal end of the latter is brought out as a single-barrel colostomy after removal of the intervening segment of bowel. Many of the patients who had undergone the Hartmann type of operation were found to be alive and well many years afterward and without evidence of return of the growth in the portion of the rectum which remained. In reviewing many specimens removed in this manner I was impressed by the fact that the site of amputation in the rectosigmoid or rectum was invariably in close proximity to the cancerous process. Could it be then that carcinoma in this region or segment of bowel rarely if ever spread downward? A careful study of the literature revealed to me that only in rare instances did carcinoma spread downward into the lymph nodes farther than 2 cm. and that when spread of such type did occur the proximal lymphatics were blocked by the carcinomatous process. With this deduction then as a justifiable basis, I began carrying out the so-called low anterior resection with re-establishment of the continuity of the bowel. Lesions occurring from 6 cm. to 20 cm. from the anal margin may be suitably treated by the operation about to be described.

TECHNIC OF LOW ANTERIOR RESECTION FOR CARCINOMA OF THE LOWER SIGMOID

The abdominal cavity is opened by means of a long, low left rectus type of incision and an exploratory procedure is carried out. The patient is in deep Trendelenburg position. First the liver is palpated for distant metastasis. Next the colon, beginning with the cecum, is examined to rule out the possible coexistence of other malignant lesions. The low sigmoidal lesion is palpated. If resection is thought to be feasible, the procedure is begun by first incising the fused lateral peritoneum from near the splenic flexure of the colon down to the pelvic peritoneal fold. The left ureter is identified and isolated. Next, the posterior parietal peritoneum is opened mesially at a point immediately cephalad to the superior hemorrhoidal

vessels. The mesial peritoneal incision is extended downward and along the base of the mesosigmoid and curved around the rectovesical or rectocervical neck. The entire pelvic colon, rectosigmoid and upper rectum are then mobilized by freeing the mesosigmoid from the sacrum, beginning at the sacral promontory and extending to the tip of the coccyx, by means of sharp and blunt dissection. The rectal ampulla is next mobilized from the vagina or seminal vesicles and prostate. In rectosigmoidal cancer situated at the pelvic peritoneal fold it is necessary, in order to obtain satisfactory mobilization, to divide and ligate the lateral rectal stalks or ligaments, which contain the middle hemorrhoidal vessels. Complete mobilization of the entire pelvic portions of the colon and upper rectum having been obtained, the superior hemorrhoidal vessels are next divided and ligated, as are the vessels in the mesentery of the distal portion of the descending colon. The latter is then divided between Payr clamps.

Long, especially constructed curved rubber-covered clamps are then placed across the bowel, usually across the upper portion of the rectum, or as far distal as possible from the lower margin of the growth. The bowel is now divided between the clamps and the pelvic colon containing the tumor is removed. The descending colon, already sufficiently mobilized, is brought down and anastomosed as an open end-to-end procedure. Chromic catgut is employed. Five grams (75 grains) of sulfabiazole are sprinkled into the hollow of the sacrum. A long Penrose cigaret drain is employed, one end being inserted into the sacral hollow near the tip of the coccyx and the other end being brought out through the lower end of the abdominal incision. This drain is lifted out—not pulled out—on the eighth or ninth postoperative day. The lateral and mesial layers of the posterior parietal peritoneum are sutured to the edges of the bowel, thus obviating any defect in the pelvis. The suture line of the anastomosis is kept intraperitoneally, if possible; however in low sigmoidal lesions this sometimes is impossible. Thus, the resection and re-establishment of continuity of the bowel have been carried out.

Since such anastomoses are difficult it is my practice at present as in the past to establish a temporary loop type of transverse colostomy. This is accomplished by bringing a small segment of the transverse colon to the exterior in the upper end of the primary incision. This segment of bowel is held in place by means of a rubber-covered glass tube passed beneath the gut through its mesentery. The abdomen is then closed about the loop of exteriorized colon. The latter is opened by means of cautery the day following resection. Such colonic stomas may be closed within three or four weeks following resection. Spur-crushing clamps are employed prior to closure of the stomas in about 75 per cent of the cases. An intraperitoneal type of closure always is employed.

During the years 1930 to 1943, inclusive, I carried out low anterior resection in slightly more than 500 cases. Of this number, 340 patients had no evidence, on abdominal exploratory operation, of distant metastasis even though there was nodal involvement adjacent to the primary lesion in many of the cases. It is my opinion that one should consider that resection in these 340 cases was employed with the hope and idea of "cure." The distance of the lesion from the anal margin (estimated during proctoscopic examination) ranged from 6 cm. to 20 cm. In ninety cases the lesions were

from 6 cm. to 10 cm. from the dentate margin. In the remaining 250 cases the cancer in the rectosigmoid and sigmoid was at a distance varying from 11 cm. to 20 cm. from the anal margin.

The mortality rate per patient in the earlier operations varied from 9 to 13 per cent. It is of special interest, I think, to note that since the use of sulfonamide drugs the hospital mortality rate has dropped dramatically. For example, from 1941 to 1943, I carried out 184 conservative low anterior resections with two deaths. In one case, the cause of death was a type III pneumonia; in the other, death was due to coronary disease.

Some well-known and able surgeons doubt the value of sulfonamides. The work of Poth and Knopp, substantiated clinically by Benson and me, proves I believe beyond doubt that the preoperative use of sulfasuxidine or sulfathaladine, plus the employment of sulfathiazole at the completion of each operation, has greatly diminished the incidence of infection, thus lowering morbidity and mortality. Preoperatively, sulfasuxidine or sulfathaladine is administered over a three day period. A total of 720 grains (48 gm.) is given orally in divided doses at four hour intervals. Also, a nonresidue diet, high in carbohydrate, is employed. Gentle catharsis is brought about by means of sodium phosphate administered during the first two days of preoperative management. Two to four drams (8 to 16 gm.) are given every four hours. Also, during this period (two days) the rectum is gently irrigated with saline solution twice daily. On the third and final preoperative day 2 fluidrams (7 c.c.) of paregoric are given each three hours.

At the completion of resection and closure of the colonic stoma, 5 gm (75 grains) of sulfathiazole are placed in the abdominal cavity near the site of the anastomosis.

The five-year survival rate in 272 cases in which I have carried out the two-stage low anterior type of resection for cancer of the low sigmoid with re-establishment of continuity of the bowel is 67.7 per cent, which I believe compares favorably with any type of procedure, including those operations which necessitate permanent colostomy.

RECTALGIA ASSOCIATED WITH INTESTINAL DISEASES: SYMPTOMATIC TREATMENT*

J. ARNOLD BARGEN

Among the most trying conditions encountered in the management of intestinal disease is the anal discomfort which so frequently occurs as a major complaint. This discomfort is trying not only for the patient but for the physician as well. Frequently the anal condition so overshadows the basic problem that much effort is wasted and valuable time is lost by directing all attention to the local anal discomfort instead of to the more serious and important disease in more proximal segments of the bowel.

* Abstract of paper published in full in *Minnesota Medicine*, 37, 361-362 (Apr.) 1948

However, experience has taught physicians that it is unwise to direct all the attention to the care of the intestinal disease, for the patient's comfort inevitably assumes an important place in the efforts to control a severe infectious intestinal disease or even the unpleasant sensations associated with the irritable bowel syndrome. Both may be associated with very uncomfortable anal tenesmus or other forms of rectalgia. Once the anal discomfort is controlled, or at least ameliorated, the major problem may be attacked more leisurely or at least with greater confidence from the standpoint of both the patient and the physician.

One may actually be surprised to see a severe diarrhea subside or lessen with the control of a patient's anal disorder, albeit this may have little direct bearing on the treatment of the disease causing the diarrhea. It is rarely wise to indulge in any reparative anal surgical procedure in the presence of intestinal disease but the importance of establishing anal comfort sometimes by the most simple means cannot be overrated. The need for control of anal discomfort has often assumed such major proportions

TABULATION

EFFECT OF RECTAL SUPPOSITORIES ON RECTAL DISCOMFORT IN CHRONIC ULCERATIVE COLITIS WITH RATHER SEVERE DIARRHEA

CASE	Suppositories used, days	Decrease in stools in 24 hours	Rectal discomfort
1	9	7 to 3	Relieved
2	9	6 to 2	Pain and soreness relieved
3	13	13 to 9	Slight soreness relieved
4	8	8 to 4	Slight soreness. No improvement
5	4	5 to 3	Relieved

that many symptomatic measures have been invoked including hot sitz baths, anal irrigations and a variety of local medicaments. It has long been known that ethyl aminobenzoate (benzocaine) has a particularly soothing effect when applied to the anal region of these sufferers. The problem of the method of its application, however, has not been easy. When prepared in the form of a rectal suppository it can be readily inserted by the patient himself. A suppository containing a soothing mixture of benzocaine, oxyquinoline sulfate, balsam of Peru and ephedrine hydrochloride in cocoa butter has proved suitable.*

Three groups of symptoms in as many types of patients have been particularly helped by this type of suppository: those patients with the anal tenesmus and rectalgia associated with the irritable bowel syndrome, those with the misery of severe anal infection and those with the diarrhea of infectious intestinal disease. In a group of patients who were afflicted

* Material used in this study was rectal medrone, supplied by The Medicone Company, 223 Varick Street, New York City, New York.

with chronic ulcerative colitis and who had rather severe diarrhea, decrease in the number of stools occurred in at least half the cases after use of this type of suppository. The tabulation illustrates this change in a small group of patients. Similar results have been obtained in a much larger series of cases.

Any relief due to medication of this type is purely symptomatic. However, it becomes much easier for the physician to control the other more serious lesion after the patient's suffering from anal discomfort has been wholly or partly relieved.

There may be other substances the use of which will result in similar relief. In this study, ethyl aminobenzoate (benzocaine) in a suitable formula in the form of a suppository has been of striking help in allaying anal discomfort. It is likely that patients with other painful anal conditions might be benefited by the use of such a suppository.

MARKED ABDOMINAL BLOATING NOT DUE TO GAS BUT TO A NEUROSIS OF THE ABDOMINAL WALL*

WALTER C. ALVAREZ

Years ago I began to see that in the case of certain nervous or psychopathic women who bloated until they looked decidedly pregnant, the cause could not be gas. Why? Because (1) when the abdomen was distended it was not particularly tympanitic; (2) as the swelling went down, sometimes suddenly, there was no passage of flatus, and (3) when a roentgenogram was made of the big abdomen it could be seen that there was no excess of gas in the stomach or bowel. That there was no organic disease in the abdomen was indicated by the fact that in almost every case several exploratory operations had failed to reveal anything significant. A number of organs such as appendix, gallbladder and uterus had been removed but none of this operating had resulted in any permanent relief.

My recent review of the literature showed that the disease has been described many times before, usually under the heading of phantom tumor, phantom pregnancy or pseudocyesis. A number of the men who wrote about the disease came to see, as I did, that the syndrome could not be due to flatulence but must be due to a neurosis of the muscles lining the abdominal cavity. Several noted that with an anesthetic the tumor would disappear in a moment, without the passage of flatus, and would come back again as soon as the effects of the anesthetic wore off.

I here report briefly seventy-four cases of neurotic bloating. A more complete report will be published later, together with a review of the literature. There are several varieties of the syndrome, some severe, painful and disabling, and others in which the distention is mild and incidental to other more serious troubles. In a few cases there is severe constipation or symptoms strongly suggestive of acute intestinal obstruction. In some cases,

* From the Transactions of the Association of American Physicians 67:50-61, 1917

However, experience has taught physicians that it is unwise to direct all the attention to the care of the intestinal disease, for the patient's comfort inevitably assumes an important place in the efforts to control a severe infectious intestinal disease or even the unpleasant sensations associated with the irritable bowel syndrome. Both may be associated with very uncomfortable anal tenesmus or other forms of rectalgia. Once the anal discomfort is controlled, or at least ameliorated, the major problem may be attacked more leisurely or at least with greater confidence from the standpoint of both the patient and the physician.

One may actually be surprised to see a severe diarrhea subside or lessen with the control of a patient's anal disorder, albeit this may have little direct bearing on the treatment of the disease causing the diarrhea. It is rarely wise to indulge in any reparative anal surgical procedure in the presence of intestinal disease but the importance of establishing anal comfort sometimes by the most simple means cannot be overrated. The need for control of anal discomfort has often assumed such major proportions

TABULATION

EFFECT OF RECTAL SUPPOSITORIES ON RECTAL DISCOMFORT IN CHRONIC ULCERATIVE COLITIS WITH RATHER SEVERE DIARRHEA

Case	Suppositories used, days	Decrease in stools in 24 hours	Rectal discomfort
1	9	7 to 3	Relieved
2	9	6 to 2	Pain and soreness relieved
3	13	13 to 0	Slight soreness relieved
4	8	8 to 4	Slight soreness No improvement
5	8	5 to 3	Relieved

that many symptomatic measures have been invoked including hot sitz baths, anal irrigations and a variety of local medicaments. It has long been known that ethyl aminobenzoate (benzocaine) has a particularly soothing effect when applied to the anal region of these sufferers. The problem of the method of its application, however, has not been easy. When prepared in the form of a rectal suppository it can be readily inserted by the patient himself. A suppository containing a soothing mixture of benzocaine, oxyquinoline sulfate, balsam of Peru and ephedrine hydrochloride in cocoa butter has proved suitable.*

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different from those described here, a woman will be sure she is pregnant, and she will remain bloated for months, perhaps with amenorrhea, morning nausea and enlargement of the breasts.

DEFINITION

The essential point in all the cases here described is that the bloating was not due to gas in the digestive tract but rather to a peculiar contraction of the muscles lining the back and sometimes the top of the abdominal cavity. This contraction, associated often with the assumption of a lordotic posture, appeared to throw the abdominal contents forward and somewhat downward toward the pelvis. In the type of case here described, the patient at first tended to float only on occasional days. The swelling usually came up slowly during the day and went down during the night, but sometimes it came up suddenly and sometimes it remained for several days. In none of the cases described here did either patient or physician suspect pregnancy.

THE MECHANISM OF THE BLOATING

When it became clear to me that in these cases the distention was not due to gas, the next question was, Might it be due to a massive angio-neurotic edema of the intestine? Somewhat in favor of this view was the fact that in seven of my cases the woman tended at times to float all over with a poorly explained edema. But that edema of the abdominal contents was not the explanation for the bloating soon became obvious when I saw several women distend markedly in a moment or in a few minutes and then go flat either instantly or in a few minutes after (1) the induction of spinal or pentothal or ether anesthesia; (2) blockage of the splanchnic nerves with an injection of procaine; (3) the onset of an attack of vomiting, or (4) a hypodermic injection of morphine. Because I could not imagine any way in which the volume of the abdominal contents could be so suddenly much increased or so suddenly restored to normal, I concluded that in most cases of this form of bloating there is no increase in the volume of the abdominal contents. About the only other possibility is that blood might pour into much dilated blood vessels in the abdomen but that does not appear likely.

Along the way it was observed also that many of the patients, most of them women, when bloated, were more than usually lordotic, and this had a marked effect in pushing the abdomen forward. Just as one can pull in one's abdominal muscles one can also push them out. As was to be expected from this, when one of those markedly bloated women was made to lie supine, especially with the knees up, she generally looked much less bloated and she might even go flat. If placed on her side with her thighs flexed on the abdomen as for a spinal puncture, the lordosis was overcome, and with this, even a badly distended abdomen was likely to go flat and soft. Usually, in such cases, the moment the woman got up and slumped into her old, markedly lordotic posture her bloating came right back.

Curiously, in some of these cases the abdominal wall was hard, but in others it was soft. A feature which helped convince me that this syndrome is due to a neurosis of the abdominal wall was the discovery of several cases in which the bloating or the contraction of the abdominal muscles involved only half of the abdomen or only one quadrant. In the case of one

woman the contractions would come in only short segments of one rectus abdominis muscle. In another case it was doubtless significant that with the cramping of the abdominal muscles there was cramping of the muscles of the arms and legs.

Interesting also was the fact that in a few cases the diaphragm could be seen with the roentgenoscope to be involved in the spasm. It descended as far as it could go and then moved but little. In other cases I could not see that the diaphragm descended abnormally. Even if it had it could not have produced all the bloating. Because of the cervical innervation of the diaphragm, so far removed from the innervation of the other abdominal muscles, it seems all the more probable that the center that gives rise to disturbance is up in the brain.

I admit that in some cases, especially when there was no marked lordosis or no marked flattening when the patient lay down, I was not sure as to the mechanism that produced the bloating. All I was sure of was that there was no excess of gas in the abdomen. There appear to be variations in the technic by which a neurotic woman can produce a protuberant abdomen.

SYMPTOMS

Many of the patients in the attacks suffered from abdominal pain, sometimes so severe that they walked the floor. Because of this, a few became habituated to morphine. In some the pain was constant, in others it was rhythmic, in still others it was only a feeling of tension arising apparently in the contraction of the muscles of the abdominal wall. In a few cases the main difficulty was the sense of embarrassment because of the appearance of pregnancy.

In all but a few cases, during the attack intestinal contractions appeared to be quieted. Intestinal gurgles were faint or absent, the bowels rarely moved, and there was rarely any passage of gas. Most of the women, however, could eat and digest while bloated.

Quite a few of the women were nauseated in the spells, and a few sometimes vomited. Most of them were constipated but it was clear that constipation was not the only cause of the trouble. Curiously, some got relief if the bowels did not move for several days; they even said they thought they would be well if they never had to go to the toilet. Evidently, in these cases defecation was a trigger that set off an attack of spasm in the abdominal muscles.

Most of the patients had a good or a fair digestion between the attacks. Curiously, in the case of the women, menstruation was rarely a factor in bringing on the spells.

A number of the women, in spite of all their suffering, tended to gain in weight.

Interval between Attacks.—As is the case with many neuroses, with the passage of years the interval between attacks tended to shorten until the woman was bloating practically every day.

Terminal Gurgle.—In a number of the cases, the attack usually terminated shortly after the patient heard a peculiar gurgle in the abdomen. This suggested that the "storm" which produced the contractions of the abdominal muscles also kept the bowel quiet.

THE TYPE OF PERSON WHO BLOATS

In the series of seventy-four cases there were sixty-nine women and five men. This type of sex distribution alone indicates a purely functional origin for the disease. Twelve of the women were single and most of these were too psychopathic, asexual or physically handicapped to get married. Most of the married women were highly nervous, neurotic, psychopathic or unhappy. A number suffered at times from definite hysteria. One was occasionally hypomanic, and several had spells of depression. Many were relatives of the insane, and many were constitutionally inadequate with poor pelvic organs, they were hypersensitive and overly reactive, and their nerves were playing tricks with them. A third of the women suffered or had suffered from migraine, but my impression is that the syndrome of bloating is not simply an equivalent of migraine.

Many of the women were decidedly allergic and sensitive to many foods, but this appeared only to be a complicating factor. Certainly I never cured one of the patients with an elimination diet. In many, the overly sensitive digestive tract appeared to be a trigger area for the production of the neurotic contraction of the abdominal muscles.

The Men Who Bloat.—There were five men whose bloating appeared to be typically muscular in type, and all showed signs of neuroticism.

THE RESULTS OF EXAMINATION WERE NEGATIVE

Practically all of the patients were thoroughly examined many times by good internists, but nothing significant was ever found.

THE FIRST ATTACK

In a number of cases the first attack could be traced to an unhappy early marriage, a divorce, or some other trying experience. The disease commonly began in youth, often around the age of seventeen.

THE EXCITING CAUSES

Many of the bloaters knew that their attacks were likely to come with any excitement, annoyance or unpleasantness, or from much standing or walking, or anything that produced fatigue. Many noted also that any large meal was likely to produce the distention. Some got along fairly well if they ate just enough to keep them alive, and some could go out in the evening with safety if they would eat nothing all that day.

That the eating only touched off a trigger in stomach or bowel was indicated by the fact that many of the persons bloated the minute they drank a glass of water, ate a few mouthfuls of food, took an enema or defecated.

TREATMENT, OR MODE OF RELIEF

Many of the patients learned that they could get some relief by lying down and resting. Otherwise, with the exception of a hypodermic injection of morphine, dilaudid or demerol, there was practically nothing that would give them any relief. The bloating which came up slowly during the day usually went down spontaneously during the night.

Operations.—As noted before, no operation of any type ever cured the patient. Even the removal of a diseased gallbladder only helped somewhat. One woman wrote that after leaving the Mayo Clinic she underwent a lumbar sympathectomy, later a left phrenicotomy, and still later a bilateral splanchicectomy without any benefit. Evidently, the cause of the trouble is not to be found in the abdomen; it almost certainly is in the central nervous system. One important point is that, whenever during the anesthetization of one of these patients the "tumor" disappears, any proposed operation should be cancelled.

PROGNOSIS

Unfortunately, I was not able to keep in touch with many of these patients after they left the clinic. However, in many cases I could look back and see that the disease had been giving trouble for from five to thirty years. I did learn through correspondence that in a few cases the bloating practically stopped when the patient's life became easier or when she adjusted well to an unpleasant situation.

THE IMPORTANCE OF PREOPERATIVE AND POSTOPERATIVE CARE IN INTESTINAL SURGERY*

CLAUDE F. DIXON

From the beginning, the greatest single factor in the cause of death in intra-abdominal operations has been infection. The same is true today! This statement has been confirmed time and again at autopsy.

During the past six or seven years, however, the morbidity and mortality rates in intestinal surgery have been reduced considerably. What is the reason for this? It is the opinion of my colleagues and myself that the employment of bacteriostatic agents and antibiotics is the answer. In the beginning, permit me to say that I am fully aware of the fact that the agents just mentioned have been used and are still frequently used empirically and that many patients so treated undoubtedly would have recovered without their employment.

It is my intention in this presentation to emphasize the apparent effect of certain sulfonamides, penicillin and streptomycin on patients who have undergone intestinal operations. Our over-all hospital mortality rate has decreased from about 15 per cent to less than 5 per cent (on the basis of patients, not operations) since the employment of sulfasuxidine (succinyl-sulfathiazole) prior to operation has become routine. As is well known, this sulfonamide is poorly absorbed by the blood stream. Its effect, as demonstrated by Poth and others, is to decrease appreciably the number of coliform organisms in the feces.

Until recently it was our custom to administer preoperatively to patients who were to undergo an intestinal surgical procedure a total of 720 grains

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place 5 gm. of sulfathiazole in the peritoneal cavity at the completion of a resection of the bowel.

The value of sulfasuxidine in intestinal surgery has recently been re-emphasized by Poth. He demonstrated, in intestinal operations carried out in dogs, that if an end-to-end type of anastomosis, open method, was employed after preoperative administration of sulfasuxidine for ten days the site of the anastomosis healed rapidly leaving only a faint hairline type of scar where the bowel ends healed. Microscopic studies of sections made through these sites of anastomosis were characterized by evidence of rapid formation of fibroblasts. A high mortality followed similar intestinal resections performed by the open method of end-to-end anastomosis when preoperative preparation with sulfasuxidine was not carried out, and in the animals that survived there was an ugly ulcerating scar at the site of the anastomosis. Microscopic study of sections cut through these scars revealed only a few fibroblasts.

MESENTERIC THROMBOSIS EXPERIMENTALLY PRODUCED

Poth further demonstrated in studies on animals that if sulfasuxidine was administered for ten to twelve days prior to ligation of the mesenteric vessels, 80 per cent of the animals survived. Extensive necrosis of the intestine was found at autopsy in the 20 per cent which died. By frequently opening the abdominal cavity of the animals that recovered (80 per cent) it was observed that marked venous engorgement of the intestine occurred and this was followed by formation of a plastic exudate; also it was noted that the life of the segment of bowel, and even the life of the animal itself, depended on rapid formation of blood vessels between the segment deprived of blood supply and an adjacent organ such as another segment of bowel or the omentum. At the time these animals were killed the segment of bowel which had been deprived of its vascular supply appeared normal except that it firmly adhered to the adjacent normal structure previously mentioned. When similar experiments were carried out on animals without preparation with sulfasuxidine, 80 per cent died in four days because of extensive necrosis of the intestine.

Progress in medicine is slow and perhaps it should be so. Many surgeons still are of the opinion that certain sulfonamide and antibiotic substances are useless or of no value, for example, in intestinal resections. Their cry is: If good technic is employed, good results will be obtained. According to my knowledge, all who are interested in surgery do not now, or never have, argued against good surgical technic; it is my belief that those who argue against the proper employment of bacteriostatic agents and certain antibiotics are viewing facts through jaundiced eyes.

THE DELAYED ONSET OF "THREE MONTHS" COLIC IN PREMATURE INFANTS*

PAUL P. PIERCE

So-called three months' colic manifested by severe, prolonged, paroxysmal crying in infants during the early weeks after birth is a well-recognized problem among practicing physicians. Despite many advances in methods of infant care, there has been little accomplished in adequately explaining the cause of this condition or its prevention or treatment.

It is well recognized that this type of behavior is seldom manifest in nurseries for newborn infants although some infants seem to give indications of potentialities for colic by their excessive irritability and their unusually large food requirements. This is seldom enough to warrant the prognosis that excessive crying will occur after dismissal to the home. It has been noted that full-term infants frequently begin to cry in increasing amounts a few days after going home from the newborn nursery. In the experience of my colleagues and me, the onset is usually when the infant is from two to three weeks of age. As is well recognized by both physicians and mothers, the symptoms are likely to end spontaneously when the infant is about three months of age. This characteristic in the time of onset and in the duration of the symptoms would seem to be most adequately explained by considering that a developmental factor is at least partially responsible for the disturbed physiologic mechanism which causes the symptom complex.

Recently, we have observed with interest the course of paroxysmal crying in a number of premature infants. It has been noted that the onset was delayed for a period of time approximating their degree of prematurity. This has been observed even in an infant weighing 2½ pounds (1.1 kg.) at birth whose period of hospitalization in the newborn nursery totaled sixty days.

In each case, the infant, who previously had been quiet and progressing normally, manifested excessive crying when approximately two weeks older than the expected date of his delivery. This has not been explainable on the basis of improper feeding technique nor by hunger. The infants were allowed adequate caloric intake. The crying seemed to appear when the infants had reached a certain state of maturity and was not simply the "awakening process" observed normally as premature infants grow older.

My associates and I have no proved explanation for these observations. Until more is learned about the pathogenesis and pathologic physiology in colic, perhaps an adequate answer will not be available. While many views have been expressed as to the most likely cause of the condition, no one of them has proved to be entirely satisfactory in itself. Such factors as under-feeding, overfeeding, improper feeding technique, gastro-intestinal allergy, autonomic nerve imbalance and others are probably partially responsible either alone or in combinations in many of the cases. Because of the observed time of onset and duration of symptoms in both full-term and premature infants, it is our belief that a developmental factor also contributes to the cause. The nature of this factor is not known but it would

* Abridgment of paper published in full in the *American Journal of Diseases of Children*, 75: 190-192 (Feb.) 1914

seem reasonable to assume that it may be primarily related to the state of maturity of some part of the nervous system. Further basic study concerning these points is needed.

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GENITO-URINARY DISEASES

THE USE OF STREPTOMYCIN IN THE TREATMENT OF TUBERCULOSIS OF THE URINARY TRACT*

EDWARD N. COOK AND LAURENCE F. GREENE

Approximately two and a half years ago, following the discovery by Waksman of a new antibiotic, streptomycin, we began the clinical investigation of the use of this agent in cases of tuberculosis of the urinary tract. In view of the prolonged period of investigation which we felt would be necessary to carry out such a study, it did not seem wise or safe to deny any patient who had tuberculosis of the kidney the benefits to be obtained from operation. In cases of unilateral renal tuberculosis when the other kidney was normal and free of the disease, treatment remained the same as previously, that is, nephrectomy of the involved kidney. Consequently, study of the effects of streptomycin in tuberculosis of the urinary tract has been carried out only in that group of patients who were suffering from renal tuberculosis in both kidneys or in a solitary kidney, the other having been previously removed for the same disease. It is still much too early to present any positive conclusions as to the results and at this time we wish to report only our experiences to date for your consideration.

Schatz, Waksman, Feldman, and Hinshaw have demonstrated in the laboratory the antibacterial effect of streptomycin *in vitro* and *in vivo*.

Our entire group is comprised of fifteen patients, ten of whom were treated in the hospital and five as outpatients. Six had tuberculosis of a solitary kidney. Three had tuberculosis of one kidney and a nonfunctioning kidney on the other side; presumably autonephrectomy had been carried out. In six cases bilateral lesions were present.

Streptomycin was administered intramuscularly in all cases. Experience taught us that a daily dosage of 1 to 2 gm. was the most useful. The larger dose of 2 gm. daily has not been used routinely but in a few cases was tried for a short period. For patients in the hospital the daily dose was equally divided and given at intervals of three, four, or six hours. For the outpatients, the total daily dose was given in either one or two injections. The total amounts of the drug given have varied in each case. The shortest period that treatment was given was one month and the longest period was two and a half years. In the latter case, treatment was intermittent but a total of approximately 300 gm. of streptomycin has been given.

Any accurate evaluation of the results obtained is difficult. We have attempted to watch the clinical symptoms, urinary findings and cystoscopic and urographic data, and from these have observed certain trends. They

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have not been constant and do not follow any set pattern. Let us first consider the symptoms.

As all physicians know, a patient suffering from renal tuberculosis rarely complains of any difficulty referable to the kidneys. Vesical symptoms, such as burning and frequent urination, dysuria and hematuria, are common. Such symptoms were noted in all our cases, although their degree varied considerably. Some patients noted considerable improvement in their symptoms. Others experienced no improvement. When improvement was noted, it was striking and we can say that these patients have been completely relieved and for the most part have remained so. In those cases in which frequency was not relieved we cannot help but wonder whether the contracture of chronic tuberculous cystitis is irreversible and even though active disease may be eradicated the chronic small fibrotic bladder of reduced capacity will remain.

Cystoscopic examination was carried out in all cases before treatment and in a good percentage of the cases during and after treatment with streptomycin. In more than three fourths of the cases definite improvement in the appearance of the bladder was noted after treatment and in half of the cases in which vesical ulceration was present before treatment we noted definite healing of the ulcers.

Pyuria was materially reduced in almost all cases while treatment was being given; this reduction took place gradually. However, the usual course was a return of the pyuria when medication was stopped. The urine of two patients has remained microscopically negative for tubercle bacilli. In all cases the urine was stained to demonstrate acid-fast bacilli and examined repeatedly in a search for *Mycobacterium tuberculosis*. The Ziehl-Neelsen as well as the auramine stain was used, and it is of interest that while the patients were under treatment the former stain usually first indicated an absence of acid-fast bacilli in the specimen examined and later the auramine stain did. This was true in most cases even though positive results for tuberculosis continued to be obtained from inoculations of guinea pigs. The smears of the urine revealed *Mycobacterium tuberculosis* again after treatment with streptomycin was discontinued.

As all know, the most important test in the treatment of renal tuberculosis is the inoculation of guinea pigs. In four cases in our series results of this test were negative. Two patients have had negative results from inoculation of five sets of guinea pigs each; one patient has had negative results from two sets, and the other from only one. The last patient did not return for further study. The patient who has had negative results from two sets of inoculations is most interesting as microscopic examination of urine for acid-fast bacilli gives negative results but a marked pyuria and hematuria continue, and cystoscopic examination still reveals ulceration of the wall of the bladder.

We have had the opportunity to study five kidneys microscopically after treatment with streptomycin. Nothing unusual in the form of a reparative process was noted that could be definitely ascribed to the administration of this drug. In one kidney an unusual fibrotic process was seen, but the actual significance was not determined.

The clinical results obtained have been mentioned and supplementing these particular studies we can say that we consider that three patients

have not been constant and do not follow any set pattern. Let us first consider the symptoms.

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have definitely had their disease arrested as manifested by relief of all symptoms and negative findings on urinalysis, microscopic study of the urine and from inoculation of the urine into guinea pigs. As previously mentioned, negative results of study of urine and inoculation of guinea pigs have been obtained in another patient, but her clinical picture is unchanged. Eight patients are still undergoing treatment, all of whom have the disease but are seemingly improved. Three patients have died, one from a miliary tuberculosis following cystoscopic examination and the other two from renal insufficiency some eighteen months after first receiving the drug.

Before this discussion is closed, it would seem fitting to make a few remarks concerning the sensitivity of the tuberculous organism to streptomycin. Waksman, Youmans, Feldman, and their associates have definitely shown that cultures of tubercle bacilli from untreated tuberculous patients are resistant to only 0.08 to 0.02 micrograms of streptomycin per milliliter of medium, and the majority are resistant to 0.15 micrograms. Their further studies have shown that following therapy with streptomycin the resistance of the tubercle bacilli to the drug may increase 500 to 1,000 times. Karlson and Feldman have been able to demonstrate that this increased resistance will persist when the organisms are passed through guinea pigs again. The persistence of the acquired resistance makes one speculate a bit as to whether or not there has been any active change in the resistance of the organism or whether the sensitive strains have been eradicated and only the resistant strains remain. This problem is being studied at the present time.

In conclusion, we wish to state that the efficacy of streptomycin in destroying tubercle bacilli in the urinary tract is still not established. We believe that the administration of the drug in cases of tuberculosis of the urinary tract does have a beneficial effect and in three of our cases the disease has been arrested. Treatment with this drug in such cases is not a substitute for surgical treatment but may be a helpful adjunct.

To date the results are not brilliant but are encouraging enough to suggest the need of continued study.

EPITHELIOMA OF THE PELVIS OF A SOLITARY KIDNEY TREATED BY ELECTROCOAGULATION*

DEWARD O. FERRIS AND RICHARD V. DAUT

The case to be presented is that of an epithelioma of the pelvis of a solitary kidney, which we treated by pyelotomy and high frequency electrode coagulation. A review of the literature shows the treatment in this case to be without parallel, its counterpart existing only in the treatment of papillary tumors of the bladder.

The patient, a sixty-one year old South American man, entered the Mayo Clinic June 6, 1946, complaining of continuous gross hematuria of six months' duration. The past history was noncontributory. One and a half years previous to his coming to the clinic he had first

* From *The Journal of Urology*, 59:577-579 (Apr.) 1948.

noted bloody urine but this condition had subsided spontaneously after four days. The second episode of bleeding had begun six months before admission to the clinic and had continued unabated. No clots had been noted in the urine. No history of renal colic could be elicited. The patient had noted a loss of 30 pounds (13.6 kg) during the past six months, as well as progressive weakness and dyspnea on exertion.

Physical examination revealed a pale, edentulous white man. No masses were palpated in the abdomen, heart and lungs were normal, the prostate was normal to palpation by rectum and there was pitting pedal edema, grade 1 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition).

Laboratory examination of the urine revealed a specific gravity of 1.012, alkaline reaction, absence of sugar, albuminuria, grade 4, erythruia, grade 5, and pyuria, grade 1 (18 cells per high-power field). Examination of the blood revealed the concentration of hemoglobin to be



Fig. 32.—Retrograde pyelogram showing hydronephrosis associated with a tumor of the renal pelvis in a solitary kidney.

6.2 gm. per 100 c.c. of blood; erythrocytes numbered 2,600,000 and leukocytes 10,000 per cubic millimeter of blood. The flocculation reaction was negative. The concentration of urea was 36 mg. per 100 c.c. of blood and the sedimentation rate was 146 mm. per hour (Westergren). The blood group was AB.

A simple roentgenogram of the abdomen showed a large renal outline on the right; the left renal area was indeterminate. An excretory urogram showed dilated tips of calices scattered over the large renal outline on the right. The left was indeterminate.

Cystoscopic examination was then conducted with the patient under intravenous pentothal sodium anesthesia. The bladder was found to be filled with dark red urine but it appeared normal otherwise. Definitely hemorrhagic spurts were seen issuing from the right orifice. A 5 F. catheter was passed up the right ureter and 35 c.c. of dark red urine were aspirated from the renal pelvis. A right retrograde pyelogram was made (fig. 32) and described as showing pelvis and calices dilated, grade 3, with multiple filling defects in the renal pelvis. Catheterization of

the left ureter was not possible. As a repeat excretory urogram showed no medium visible, up to and including the ninety-minute film, in either renal area, it was felt that the left kidney had little, if any, function remaining. For all practical purposes, therefore, the case had to be considered as one in which there was a solitary kidney. A diagnosis was made of hydronephrosis complicated by a tumor of the renal pelvis. Exploration of the right kidney was advised.

Following the urologic investigation, 500 c.c. of whole blood was transfused as, owing to continuous hematuria, the concentration of hemoglobin had dropped to 4.9 gm. per 100 c.c. of blood seven days after admission.

At operation, the kidney was exposed without difficulty through a primary posterolumbar incision. It was found to be hydronephrotic, grade 3, and was enlarged to twice normal size. The ureter was explored and found to be normal. A longitudinal incision was made in the posterior aspect of the renal pelvis and a large, organized blood clot was removed. A papillary epithelioma could then be seen arising from the posterosuperior aspect of the renal pelvis and extending 1 cm. into the upper infundibulum. The greater portion of the tumor was excised along with a small segment of the site of origin. The pathologist reported this tumor to be a papillary squamous cell epithelioma, grade 2 (Broders' method), with no obvious infiltration of the renal pelvis. This being for all practical purposes a solitary kidney, it was not feasible to sacrifice any portion of it. We decided, therefore, that our best method of destroying the lesion and still maintaining adequate renal function would be to electrocoagulate the remaining portion of the tumor thoroughly. This was carried out without difficulty. A nephrostomy tube was placed through the lower calix and the incision in the renal pelvis was closed.

During the first four days after operation the patient was given 2,000 c.c. of whole blood in the treatment of his secondary anemia. The urinary output was entirely through the nephrostomy tube and measured 450 c.c. during the first four days. At this time the concentration of urea had risen to 168 mg. per 100 c.c. of blood and the carbon dioxide combining power had dropped to 37.2 volumes per 100 c.c. of plasma. Five per cent solution of sodium bicarbonate was administered intravenously to restore the acid-base balance. The output of urine on the fifth day, and subsequently, never fell below 1,500 c.c.

Fourteen days after operation the nephrostomy drainage was clear; erythrocytes were reported as "occasional" and pyuria was graded 1. At this time the concentration of hemoglobin had increased to 10.6 gm. per 100 c.c. of blood, the concentration of urea had fallen to 88 mg. per 100 c.c. of blood, the carbon dioxide combining power was 50.2 volumes per 100 c.c. of plasma and the concentration of protein was 6.7 gm. per 100 c.c. of serum. The patient was out of bed, eating well and feeling stronger than previously.

The patient continued to improve and was dismissed from the hospital on the twenty-eighth postoperative day. The nephrostomy tube was clamped and he voided normally and without difficulty. After five days of normal micturition, the nephrostomy tube was removed (forty-fifth day after operation) and the small defect where the tube had been located healed promptly. The concentration of urea was 64 mg. per 100 c.c. of blood and the carbon dioxide combining power was 45.5 volumes per 100 c.c. of plasma. An excretory urogram at this time revealed, as before, no evidence of the medium on the left and absence of renal outline. On the right, dilated tips of the calices were seen scattered over the large right renal outline. The patient was dismissed on the forty-ninth postoperative day in excellent condition.

Correspondence eight months after operation revealed the patient to be in excellent health and completely asymptomatic.

The prognosis in this case is, of course, guarded. We are well aware that the case is unusual and that the risk attending the procedure was great but we succeeded in stopping an exsanguinating hematuria and possibly effected a permanent cure.

CARCINOMA OF THE URINARY BLADDER: A PATHOLOGIC STUDY WITH SPECIAL REFERENCE TO INVASIVENESS AND VASCULAR INVASION*

JOHN R. McDONALD and GERSHON J. THOMPSON

It was felt that a study of a sizable group of surgically removed carcinomas of the urinary bladder might be worth while if the accompanying bladder were available also. Many investigations have been made on vesical neoplasms by utilization of tissue removed transurethtrally but in such studies only a portion of the underlying bladder, at most, can be studied. Information which the surgeon obtains from the pathologist is oftentimes woefully inadequate as applied to the method of treatment which should be employed in such a case. Furthermore, when surgical therapy is given such a patient suffering from a carcinoma, the factors entering into the prognosis have been vague, much more vague than in cases of carcinoma elsewhere in the body.

Several excellent studies have been reported concerning factors which govern prognosis in carcinoma of the urinary bladder. Broders in 1922 showed the influence of the factor of histologic grade on the prognosis. Further proof of the influence of the factor of grade on the survival rate of patients suffering from carcinoma of the urinary bladder is evident from the reports of the bladder tumor registry of the American Urological Association (1934 to 1936, inclusive). It is obvious that the histologic grade of a neoplasm is not the only factor of importance. This is evident elsewhere in the body as, for example, in the large bowel where it has been shown by Dukes that infiltration of the wall of the bowel and the pericolonic fat and metastasis are factors of extreme importance in the prognosis. The importance of involvement of the blood and lymphatic vessels in carcinoma of the renal pelvis, in regard to prognosis, has been stressed by one of us (McDonald) and Priestley. It was that study which stimulated the present one.

Anatomic factors have been considered in several studies on vesical tumors. Aschner in 1931 classified neoplasms of the bladder as to whether they did or did not infiltrate and as to whether they were papillary or non-papillary. On the basis of a follow-up of three years or longer, in the papilloma group 80 per cent of the lesions were arrested; in the papillary carcinoma group without infiltration, 54 per cent were arrested; in the papillary carcinoma group with infiltration, 18 per cent were arrested; and in the nonpapillary carcinoma group, 16 per cent were arrested. His conclusions were that the presence or absence of infiltration represented a reliable guide as to the gravity of the carcinoma of the bladder.

A more recent attempt to employ infiltration as a guide to prognosis in tumors of the bladder is that of Jewett in 1944. In a study of 107 cases of carcinoma of the urinary bladder in all of which the patients had come to necropsy, particular note was paid to penetration of the wall of the bladder by the carcinoma. These cases were divided into three groups. The first group included those in which the tumor was confined to the submucosa.

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No evidence of metastasis or perivesical fixation was found in these cases. The second group consisted of those in which infiltration had extended into the muscularis but not through it. There were fifteen cases in this group; distant metastatic lesions were found in one case and invasion of the lymphatics in another. The third group comprised those in which the carcinoma had invaded the entire muscle. Of eighty-nine cases in this group, metastatic lesions were present in fifty-two. In addition to these fifty-two cases, perivesical lymphatics were involved in six cases and perivesical fixation occurred in eight cases.

In our study of the anatomic factors of importance which should merit consideration in tumors of the bladder, it was decided not to employ biopsy material. It is obvious that in material of this sort the anatomic relationship of the tumor to the vesical wall cannot be determined. It was therefore decided to utilize surgical material in which the tumor had been removed along with a portion or all of the vesical wall. This meant that in all cases utilized in this study suprapubic exploration was carried out and either segmental or total cystectomy was done. Cases in which suprapubic exploration was done and in which the tumor was fulgurated without removal of a portion of the wall of the bladder were discarded. We are not attempting to analyze the usefulness of various surgical methods and, consequently, the type of operation which has been done will not be mentioned further. This material was removed during the years 1932 to 1944, inclusive. Of necessity, the lesions do not represent consecutive vesical tumors seen at the clinic because many tumors of the bladder were treated by transurethral methods, irradiation therapy or a combination of these two. Nor do they represent consecutive series of vesical tumors in which segmental or total cystectomy was done at the clinic, because in certain cases specimens have been lost or were otherwise unsatisfactory for pathologic examination.

In all cases a block was cut through the greatest diameter of the tumor including the entire vesical wall and the perivesical tissue. In some cases more than one block was cut. These were impregnated with paraffin, sectioned in the usual way and stained with hematoxylin and eosin. In those cases in which, on histologic examination, it was thought that mucus was being produced by the tumor, mucicarmine stains were employed. In these vesical tumors we had sections made through the largest diameter of the tumor, the entire musculature coat, the perivesical fat and, where possible, the adjacent normal mucosa of the vesical wall. Histologic and morphologic study of these specimens was made without any knowledge of the clinical course of the disease. All observations were made, therefore, with as little prejudice as possible. The survival rates were calculated and all pertinent data from the clinical records were tabulated by the Section on Biometry and Medical Statistics.

CLASSIFICATION

A basic principle in histopathology has been to classify carcinomas into types; namely, squamous cell carcinoma, adenocarcinoma or transitional cell carcinoma. For one reason or another this principle has frequently been avoided in the classification of tumors of the bladder. We arbitrarily have defined a squamous cell carcinoma as one in which the cells are becoming

keratinized or cornified. Since there is no special stain with which to demonstrate keratin, minor degrees of keratinization can be difficult to recognize in hematoxylin-eosin sections. Keratin stains faintly with eosin or it may be dissolved out in the various solutions, leaving clear cytoplasm. In this study, definite amounts of keratin had to be present before the tumor was classified as a squamous cell carcinoma. A carcinoma was classified as adenocarcinoma when it formed acini or produced mucus. The mucicarmine stain was helpful in identifying mucus. A transitional cell carcinoma was one which was of neither of the first two types mentioned. The majority of carcinomas of the bladder in this study were of the transitional cell type. A surprising number proved to be glandular. The majority (thirty) of adenocarcinomas were not pure adenocarcinomas but were mixed either with squamous cell carcinoma or nonkeratinizing epithelioma.

Of the squamous cell carcinomas (seventy-eight pure, sixteen mixed squamous cell and adenocarcinoma), ninety-three infiltrated the wall of the bladder and one was noninfiltrative. Of the forty adenocarcinomas, pure and mixed, all were infiltrative. The survival rate for the entire group of traced patients with these neoplasms of the bladder was 29 per cent. The survival rate for patients with nonkeratinizing epitheliomas was better than the average while the survival rate for those with squamous cell carcinoma and adenocarcinoma was poorer than the average.

Papillary or Nonpapillary Carcinoma.—We have divided carcinomas of the urinary bladder into three types: papillary carcinoma without infiltration, papillary carcinoma with infiltration and infiltrative (nonpapillary) carcinoma. This was done because in our experience this classification has been useful in carcinoma of the renal pelvis (McDonald and Priestley, 1944). Few of the carcinomas which have been of the squamous cell type, according to the term as we have defined it, have produced papillary projections. The adenocarcinomas have similarly shown lack of villous projections. The transitional cell carcinomas can be divided into those which are papillary and those which are nonpapillary.

Of 189 infiltrative nonpapillary carcinomas, 118 were either squamous cell carcinoma or adenocarcinoma or combinations of adenocarcinoma with other types. The remainder, seventy-one, have been of the transitional cell type. Some of these transitional cell carcinomas were probably of the papillary type originally but the projections had been burned off by transurethral fulguration. There is, in other words, no way of knowing how many of these transitional cell neoplasms were originally nonpapillary.

Fifty-four or 19.7 per cent of the entire group were papillary carcinomas and, on histologic examination, evidence of infiltration could be found. Some pathologists and urologists classify papillary neoplasms of the bladder into those which are benign and those which are malignant. It has been our policy to group them together. It is significant that the material in this study does not represent a consecutive series of vesical tumors and that many of the tumors in this papillary noninfiltrative group were treated transurethrally. Only a few patients have resections of the urinary bladder. It is well recognized that the majority of tumors in the bladder are of the papillary type. Obviously, in this series, that is not the case.

The third group of papillary tumors, made up of those which did not infiltrate the wall of the urinary bladder, comprised thirty-one cases or

11.3 per cent of the entire series. In other words, eighty-five or 31 per cent of the tumors under discussion were papillary while 69 per cent were non-papillary infiltrators. Histologically, in four cases in the infiltrative group the lesion was graded 1 (Broders' method). All of these were adenocarcinomas. We had, in this group, no grade 1 squamous cell carcinomas, all being grade 2 or higher. In the group of papillary carcinomas without infiltration, fifteen of thirty-one, or 48.4 per cent, were graded 1. This is the group which would be considered as benign papillomas by many pathologists. It is rare for neoplasms of this type and grade to metastasize although death may result from ureteral obstruction with subsequent infection. It is obvious that there is need for a definition as to what comprises a carcinoma of the urinary bladder. In the remaining sixteen cases of papillary carcinoma without infiltration of the wall the lesions were graded 2 or 3. In the group of papillary tumors with infiltration there were no grade 1 lesions, all being graded 2 or higher. It has been our general conception of this group that grade 1 papillary epitheliomas rarely infiltrate. Unfortunately, through a cystoscope it is often not possible to determine whether a given papillary neoplasm is or is not infiltrative.

The Depth of Involvement of the Wall of the Urinary Bladder in Carcinoma.—The survival rates in this group of carcinomas of the urinary bladder which invaded the wall of the bladder has been charted according to the depth of involvement of the urinary bladder. This group comprises those villous neoplasms which infiltrate as well as the nonpapillary infiltrating carcinomas. In all there were 243 cases in which survivals could be calculated. Of these, fifty-four belonged in the papillary group with infiltration and 189 in the nonpapillary infiltrative group. The depth to which the bladder was involved has been charted according to whether the tissue between the epithelium and the muscle was involved (this has been termed submucosa), whether the malignant tissue extended into the muscle but not deeper and whether the malignant tissue extended out to the fat. Of the entire group of lesions, 12.8 per cent penetrated only the submucosa, 53.9 per cent extended into the muscular layer and 33.3 per cent extended into the fat. When the fat is involved the survival rate drops very markedly. It is in this group that the greatest amount of vascular involvement occurs.

Invasion of the Vessels in the Wall of the Bladder.—Involvement of vessels was seen in 102 of 274 cases. Two types of vascular invasion with tumor were seen: venous involvement and perineural lymphatic involvement. Our criterion for the demonstration of a vein was that it should have a definite coat of smooth muscle. In this way, artefacts could be avoided. Therefore, when venous invasion was noted the tumor cells were enclosed within a definite coat of muscle. Small lymphatics such as are found in the wall of the bladder are not identifiable as such in histologic preparations except for the knowledge that around the nerves there is a lymphatic sheath. Therefore, when lymphatic involvement was noted it was of the perineural type.

Of the 102 cases in which vascular invasion occurred, venous invasion alone was noted in twenty-three, perineural lymphatic involvement alone was seen in sixty-four and a combination of the two was observed in fifteen. Invasion of vessels was rarely seen except where infiltrating tissue had penetrated to the deep muscular layer or perivisceral fat, particularly the

latter. This finding is consistent with the low survival rate for carcinoma of the urinary bladder which has involved the perivesical fat; when the perivesical fat has been infiltrated, the prognosis is very poor. The survival rate of our group of patients who had carcinoma of the urinary bladder without vessel involvement was 37.8 per cent. In those with vascular involvement the survival rate was 11.6 per cent. This demonstrated very graphically the influence of vascular invasion on the prognosis.

COMMENT

Several anatomic, morphologic and cytologic features are of importance in determining prognosis and treatment for patients who have carcinoma of the urinary bladder. It is important to know whether infiltration has or has not occurred. If infiltration has occurred, it is most significant to know whether the carcinoma has involved the perivesical fat or not. It would appear that groups A and B of Jewett might well be combined and labeled group A or some other arbitrary designation but that a second group consisting of cases in which invasion of the fat has occurred should be differentiated from the preceding group. This newly differentiated group might be labeled "group B." A second factor of importance is the classification of carcinoma into cell type. Transitional cell carcinoma offers a much better prognosis than squamous cell carcinoma or adenocarcinoma, whether found alone or mixed with either of the other two types. Of course, the bulk of the transitional cell epitheliomas are papillary in type, whether with or without infiltration. Another feature of importance in treatment and prognosis is the factor of involvement of vessels, which has a definite bearing on prognosis. Unfortunately, it is necessary to have adequate microscopic studies to determine the presence or absence of vascular invasion. It is impossible to determine invasion of the vessels as easily in the bladder as in the kidney because in the kidney there is, in the main, one renal vein; in the bladder there are many veins. The same holds true for nerves. In the kidney there is a concentration of nerves, in the bladder the converse is true. The importance of histologic grading of tumors of the bladder is accepted by many and, for this reason, the matter has not been discussed herein.

TOTAL CYSTECTOMY IN THE TREATMENT OF VESICAL CARCINOMA*

DEWARD O. FERRIS AND JAMES T. PRIESTLEY

During the past ten years interest has been revived in the treatment of certain types of vesical carcinoma by means of total cystectomy so that at the present time it is rather widely recognized that this procedure has a definite place, and one of importance, in the management of malignant lesions of the bladder. This recognition has been achieved, despite a certain amount of opposition to the operation, by the gradual elimination of some

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of the difficulties and hazards which have attended this procedure during past years. By no means have all of the difficulties and hazards been eliminated but they have been reduced to a degree commensurate with those which attend operations of similar magnitude for lesions of comparable seriousness in other parts of the body. Among those who have had a significant part in the development of total cystectomy should be mentioned Coffey, Beer, Lower, Wade, Quinby, G. G. Smith, Hinman, Weyrauch, D. Smith, Ewert and Dick, Graves and Thomson, McComb and Pearse, Hepler, Higgins, Jewett, Sweetser, Wilhelm and others.

The present discussion of the subject restates the problems involved, evaluates present-day success in meeting these problems and reviews our experience with total cystectomy during the past ten years. Because of the magnitude of the subject many significant details are omitted.

STATEMENT OF THE PROBLEMS INVOLVED

There seem to be five main problems which must be considered in any general evaluation of total cystectomy for vesical carcinoma. These include (1) selection of patients on whom this operation is to be performed; (2) operative procedures and technic to be employed; (3) accomplishment of a satisfactory operative mortality rate; (4) adequate preservation of renal function and avoidance of serious renal infection for years after the operation, and (5) attainment of ultimate results as regards recurrence of malignant lesions which will justify so radical a surgical procedure. Obviously there are many other considerations of somewhat lesser significance. While some of these five problems have been fairly well worked out during recent years, certain others have not and their satisfactory solution will require further time. Each of these five problems will be discussed briefly.

SELECTION OF PATIENTS

Selection of the patient for total cystectomy depends on a number of factors. Important among these are age and general condition of the patient, anatomic and functional status of the kidneys and ureters, the type, extent and location of the lesion in the bladder and the facilities and experience of the surgeon. For the present discussion of indications for total cystectomy, one might divide the prospective patients into three main categories; namely, those for whom this procedure obviously is undesirable, those for whom there is some question regarding its advisability and those for whom it appears to be indicated.

In the first category is the patient who has a small noninfiltrating lesion which can be treated adequately by transurethral measures, the one who has a lesion in the dome of the bladder that can be widely excised by segmental resection, the one who has organic disease elsewhere in the body of sufficient magnitude to prohibit a major surgical procedure, the one of extremely advanced years, and so forth. Obviously, in the treatment of patients in this category the question of total cystectomy does not arise for consideration.

In contrast, there is a large group in which the findings suggest the possible advisability of complete removal of the bladder but certain attendant features raise a question regarding either the necessity or the desirability of this operation. In this group are those who have a lesion which perhaps

might be removed or destroyed completely by some less formidable procedure. It is extremely difficult, and often impossible, for even the most experienced cystoscopist to determine the actual extent of a vesical carcinoma. This is true even though he is aided by information obtained from biopsy and complete urologic investigation. Jewett has recently emphasized the importance and significance of intramural infiltration and penetration of a vesical carcinoma perhaps through the entire thickness of the vesical wall and into the perivesical tissues. Cystoscopic examination alone certainly will not determine the actual extent of the lesion in every case. It would seem preferable in any case of an infiltrating or high-grade vesical lesion for the cystoscopist to err on the side of overestimating, rather than underestimating, its extent. In addition to the local findings in the bladder and the condition of the kidneys and ureters, the age and general physical condition of the patient may raise a question regarding the wisdom of advising total cystectomy. Obviously in this borderline group of patients the opinions of competent urologists will vary concerning the choice of treatment because of personal interpretation of the findings.

There is a third group of patients for whom we think that total cystectomy is indicated, provided that the age and general health of the patient in question are not prohibiting factors and the surgeon is experienced. It is of course true that the operative mortality rate and morbidity must be weighed against the possible end results of total cystectomy as compared with some conservative type of treatment. As one's experience with complete removal of the bladder increases, his indications for the operation may broaden because of reduced operative mortality rate. One hesitates to list indications for total cystectomy dogmatically, because they are still in the process of development and diverse opinions on this subject are expressed by leading urologists. The following indications, therefore, are mentioned with the reservation that they constitute merely a working plan on which we have been selecting patients for this operation during recent years and which may be changed in the future. These indications are: (1) a low-grade lesion with apparently minimal or moderate infiltration, provided it involves a major portion of the vesical wall and cannot be completely removed by less extensive measures; (2) a similar type of lesion which is of multicentric origin and which involves numerous regions of the bladder; (3) repeatedly recurring lesions of low grade, with or without appreciable infiltration; (4) an infiltrating or high-grade lesion which cannot be widely removed by segmental resection without interference with a uretero-vesical orifice or the vesical neck; (5) any vesical carcinoma, the complete removal or destruction of which would result in serious interference with normal vesical function. Total cystectomy rarely, if ever, seems justified as a palliative procedure. Recurrent high-grade lesions seldom are suitable for any radical surgical treatment because of extravescial extension.

OPERATIVE PROCEDURE AND TECHNIC

Operative procedures and technic will not be discussed in detail; only certain general considerations will be mentioned. Numerous different procedures and technics, now in the stage of trial, are employed currently to accomplish complete removal of the bladder. Comparable results are obtained for the most part by those who use a certain plan of procedure

with which they are familiar, although it may differ in many regards from the procedures used by others. Undoubtedly it will be some time before the technical aspects of performing total cystectomy are relatively uniform and standardized.

In general, transplantation of the ureters to the bowel is preferable to cutaneous ureterostomy and it is now known that the latter procedure seldom is necessary. With proper attention to certain technical details, a moderately dilated ureter can be transplanted to the bowel without undue hazard. In our experience at the Mayo Clinic, cutaneous ureterostomy has been performed in only 7 per cent of the 111 cases in which total cystectomy has been accomplished for carcinoma in the ten years 1937 to 1946, inclusive. However, in an additional 11 per cent of these cases, various procedures other than bilateral ureterosigmoidostomy or bilateral cutaneous ureterostomy have been employed for diversion of the urinary flow. For the most part, procedures other than ureterosigmoidostomy were employed in the earlier cases in the series and have been used less frequently during recent years. It is quite undesirable to transplant one ureter to the skin and the other to the bowel, as the patient then has the disadvantages of both these abnormal methods of urinary drainage.

The number of stages to be employed in the performance of total cystectomy is still a matter of discussion. We started using three stages, transplanting each ureter to the bowel in separate stages and subsequently removing the bladder. Later, with further experience, two stages were employed, a simultaneous bilateral ureterosigmoidostomy constituting the first stage and removal of the bladder forming the second stage. During the past three years, one stage has been used in the majority of the cases. Thus, in 1946, total cystectomy was performed in thirty-three cases and in twenty-four cases (73 per cent) a one-stage operation was employed. While the one-stage procedure is our method of choice at this time, it would not be suggested as the proper procedure until a certain amount of familiarity with the operation has been acquired.

Similarly, in our initial efforts in this field, the extraperitoneal approach was used to transplant the ureters to the bowel. When it became apparent that ureterosigmoidostomy could be accomplished with reasonable expectation that leakage at the site of anastomosis would not occur, the transperitoneal approach through a low midline incision was used. This approach has the advantages of more complete exposure of the structures involved, greater ease in the technical execution of the operation and more satisfactory alignment of the ureters and bowel. In addition, it affords an opportunity to remove the bladder at the same time through the same incision.

As regards the technical aspects of ureterosigmoidostomy, it is well recognized that it is essential to avoid angulation, tension or twisting of the ureters. The complete avoidance of any obstruction of the ureters occurring during either the early or the late postoperative period is of paramount importance. Prevention of peritoneal contamination at the time of operation from either the urinary or the intestinal tract is necessary. In general, use of a relatively simple operative technic is preferred. Our preference is for the Coffey no. 1 technic as originally described, with minor variations (figs. 33 and 34). A catheter in the ureter is used rarely and then only if a definitely abnormal ureter is transplanted. Proper preoperative

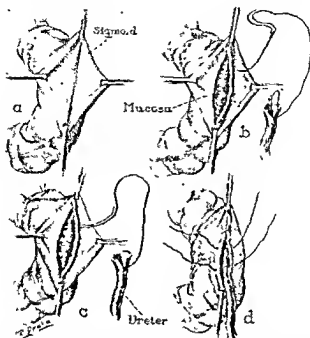


Fig. 33.—Bilateral uretersigmoidostomy, Colley no. 1 technique: *a*, the right longitudinal band is the site of incision for both anastomoses, *b*, the short end of the lead suture is threaded into the lumen of the ureter, *c*, introduction of suture to lead the ureter into the bowel, *d*, simple three suture closure of incision

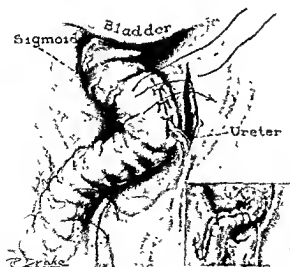


Fig. 34.—Bilateral transperitoneal uretersigmoidostomy. Both anastomoses are through the right longitudinal band of the colon.

preparation of the patient, especially adequate cleansing of the large bowel, is widely appreciated as of great importance. Likewise, postoperative care, which avoids abdominal distention, prevents accumulation of urine and feces in the sigmoid with resultant increase of intraluminal pressure, obviates a bulky stool during the early postoperative period and utilizes prophylactic chemotherapy, is essential to assure a smooth convalescence in a high percentage of cases.

A few additional miscellaneous points might be mentioned. Preliminary intraperitoneal exploration, which includes not only the local lesion but also the areas of regional lymphatic drainage from the bladder, periaortic lymph nodes and liver, should precede any final decision to remove the bladder. As mentioned previously, total cystectomy seldom, if ever, seems justifiable as a palliative procedure. It appears to us that as radical removal of the bladder can be accomplished through the suprapubic approach alone as if perineal exposure in addition were used. Drainage through the urethra, as well as the suprapubic incision, obviates necessity for direct perineal drainage. In addition to removal of all involved tissues, a wide resection of all adjacent tissues, whether or not grossly involved, is necessary to afford the best chance against recurrence. If possible, the vesical space should always be extraperitonized at the conclusion of the operation.

OPERATIVE MORTALITY RATE

It is obvious that the operative mortality rate of ureteral transplantation and cystectomy must be reasonable if this operation is to be employed with any degree of frequency for the treatment of vesical carcinoma. It probably is the experience of most surgeons that such an operative mortality rate is obtained only gradually. Our experience in this regard is shown in table 1. In some of the cases included in this table operation was performed by our colleagues, Dr. Walters and Dr. Counsellor. All cases in which total cystectomy was planned as well as those in which it was accomplished during the ten years, 1937 to 1946, inclusive, have been included. Thus, total cystectomy was planned in 119 cases but actually accomplished in only 111 cases because of eight deaths which followed ureteral transplantation in cases in which two stages were to be employed. In all, sixteen of the 119 patients died in the hospital, a mortality rate of 13 per cent. It is of some interest that the hospital mortality rate for 1942 to 1946, inclusive, was 8 per cent, as compared with a rate of 25 per cent for the previous five years, 1937 to 1941, inclusive. Undoubtedly, chemotherapeutic agents which have been developed during recent years played an appreciable part in reduction of the mortality rate during the past five years. It is anticipated that the rate of 8 per cent may be reduced in the future.

PRESERVATION OF RENAL FUNCTION

As mentioned previously, not only must recurrence of the malignant process be avoided if a satisfactory result is to be obtained after total cystectomy for carcinoma, but adequate maintenance of renal function and prevention of serious renal infection must be accomplished. In some cases in which death occurs many months, or perhaps years, after removal of the bladder, it may be difficult or impossible to determine whether recur-

rence of the malignant lesion or renal failure and infection were responsible for the fatal outcome. This is especially true if a postmortem examination is not made. Thus, a recurrence near the site of the ureteral transplantation may cause ureteral obstruction and renal failure. As near as can be determined, five of the 103 patients who survived ureteral transplantation and cystectomy subsequently died of renal failure or sepsis. While this figure probably is not accurate, it represents as fair an estimate as possible from the information available. It is thought that deaths from this cause are directly attributable, for the most part, to errors in operative technic and should gradually be reduced. A kidney which has good drainage, whether to the bowel or to the skin, seldom becomes seriously infected, except by the hematogenous route, and likewise seldom suffers from serious impairment of its function. While formation of stones may occur after ureteral transplantation, it is rare.

TABLE 1

TOTAL CYSTECTOMY*
HOSPITAL MORTALITY BY OPERATIVE PROCEDURE, 1937-1946, INCLUSIVE

Operative procedure	Patients	Hospital deaths	
		Number	Per cent
Bilateral ureterosigmoidostomy and total cystectomy.			
One stage..	30	1	3
Two stages	56	10*	18*
Three stages .	7	1	14
All cases.....	90	12	12
Bilateral cutaneous ureterostomy and total cystectomy.			
All cases	8	2	25
Miscellaneous procedures and total cystectomy.			
All cases... ..	12	2	17
Total....	110†	16	15

* Eight deaths are included after bilateral ureterosigmoidostomy prior to performance of total cystectomy.

† Removal of the bladder was accomplished in only 111 cases because of eight cases included in which death occurred after bilateral ureterosigmoidostomy.

LATE RESULTS

Our data do not permit the formation of a final opinion regarding late results after cystectomy for carcinoma. Obviously the ultimate results depend, to a great extent, on the type of case in which this operation is performed. It has only been within the last five years or so that the operative mortality rate has been reduced to a level which has permitted performance of total cystectomy in any but the most advanced and serious type of lesion. Thus, in the cases in which operation was performed in the first half of the present series (1937 to 1946, inclusive), the local lesion, almost with-

out exception, was of long duration, extensive, of high grade, often had invaded the perivesical tissues and frequently was recurrent in nature. It could not be expected that the ultimate results in cases of this type would be favorable, regardless of what type of treatment was employed. During the past five years, total cystectomy has been performed in many cases in which the lesion was of a more favorable type and it is to be expected that the results in this group will be better.

Results up to five years after operation are shown in table 2. Thus it is seen that whereas 29 per cent of patients survived three or more years after operation, only 19 per cent survived five or more years after cystectomy.

TABLE 2
TOTAL CYSTECTOMY FOR CARCINOMA. SURVIVAL RATES

Period, yr	Patients*		Lived beyond indicated period	
	Total	Traced	Number	Per cent of traced patients
1	72	68	42	62
2	56	53	23	43
3	50	48	14	29
4	44	41	8	20
5	27	27	5	19

* Inquiry as of January 1, 1947. The one-year group includes those patients who underwent operation one or more years prior to the time of inquiry (1945 or earlier); the two-year group includes those patients who underwent operation in 1945 or earlier, and so forth. Deaths in the hospital are omitted from the calculations.

As mentioned, it is thought that these results will be improved in the future. Of the 119 patients for whom complete removal of the bladder was planned or accomplished, sixteen died in the hospital. Of the remaining 103 patients, eight were in group A, fifty-nine were in group B and thirty-six were in group C, according to Jewett's classification. As might be expected, 56 per cent of the thirty-six patients in group C have already died of recurrent carcinoma, whereas only 28 per cent of the fifty-nine patients in group B and none of those in group A have died of recurrence. The prognostic importance of the extent of infiltration of the primary lesion in the bladder is obvious.

SUMMARY

Total cystectomy has gradually become recognized as an important form of treatment for certain patients who have vesical carcinoma. The main problems which have impeded acceptance of this operation are (1) selection of patients, (2) operative technique, (3) satisfactory operative mortality rate, (4) postoperative preservation of renal function and avoidance of sig-

nificant renal infection, and (5) ultimate results which command respect. Each of these problems is discussed. Some have been fairly well solved and others await solution. In 119 cases in which total cystectomy was planned or accomplished within the years 1937 to 1946, inclusive, the hospital mortality rate was 13 per cent. For the last five years of this period the rate was 8 per cent.

ROLE OF THE EXTERNAL URETHRAL SPHINCTER IN THE NORMAL BLADDER AND CORD BLADDER*

JOHN L. EVNETT, RICHARD V. DAUT AND J. HARTWELL DUNN

Considerable progress has been made in the past few years in the treatment and care of cord bladders resulting from traumatic, inflammatory, neoplastic and degenerative lesions of the spinal cord. It has been satisfactorily demonstrated, we believe, that with suitable care (which includes transurethral resection of the vesical neck in many cases), in the majority of cases, urosepsis can be eliminated and satisfactory vesical function can be established. By the term "satisfactory vesical function" we mean that incontinence is eliminated so that the patient can be kept dry, the bladder is able to empty its contents completely, leaving no residual urine, and the patient can either initiate micturition at will or has sufficient warning of impending micturition so that he has time to procure a urinal. It also stipulates that the capacity of the bladder is sufficient to allow the patient from one and a half to several hours between evacuations of urine.

The treatment of the chronic phase of neurogenic vesical dysfunction is a more involved problem. It is our opinion that transurethral resection will be necessary in a considerable proportion of cases.

We have stated in previous articles that we believe almost all true cord bladders eventually become hypertonic and trabeculated to some degree. This process seems eventually to involve the vesical neck (internal sphincter), which is simply the edge of the detrusor muscle. The spasticity and hypertrophy of the vesical neck or its inability to relax (or both) apparently acts as an obstruction at the vesical outlet and is responsible for the residual urine and vesical disability. Even though this may not be apparent within the first few months or year or so after the onset of the lesions of the spinal cord, it is nearly always apparent in cases in which the lesion has been present for a long time.

We have had a most encouraging experience with transurethral resection in cases of cord bladder. If we were to stipulate any one condition which should be present in order to insure a good result from transurethral resection, it would be the presence of a substantial amount of residual urine. Fortunately, residual urine is present in most cases. We have had considerable difficulty in distinguishing an automatic bladder from an autonomous or "nonautomatic" bladder. This is not difficult in cases in which the bladder evacuates urine at fairly regular intervals of an hour or more

* Abridgment of paper published in full in *The Journal of Urology*, 59: 439-454 (Mar.) 1948.

but in cases in which evacuation occurs more frequently and irregularly an automatic bladder is difficult to distinguish from the type of bladder which we have regarded as autonomous or "nonautomatic." In cases of the latter type of bladder, there are frequent spurts of urine which have been regarded as "overflow" or the result of arrhythmical inefficient contractions; these apparently are initiated in the detrusor muscle entirely independent of the central nervous system. We have also found it difficult to correlate the type of vesical dysfunction with the site, severity, or completeness of the lesion in the spinal cord. Our experience in this field, however, has left us with the impression that a satisfactory result is more easily achieved with transurethral resection in cases of autonomous (nonautomatic) bladder than it is in cases in which the bladder is of the automatic type. This is especially true if the lesion is sufficiently low that the abdominal muscles are still intact or partially so, in order that the patient may employ intra-abdominal tension to assist in micturition.

It is interesting to note that Head and Riddoch recognized that the most common situation encountered is a hypertonic bladder which is unable to evacuate its contents completely because of an excessively tonic sphincteric mechanism which apparently is unable to relax. This we consider to be the great underlying principle in the problem of the cord bladder; it is the reason why transurethral resection of the vesical neck is successful in a large proportion of cases. This thesis we have explained in previous communications. Recent experience has, we believe, demonstrated that not only is the vesical neck (internal sphincter) a factor, but in some cases abnormal degrees of flaccidity or spasticity of the external urethral sphincter or inability of the external sphincter muscle to relax are factors of importance which must be corrected to achieve satisfactory vesical function in the neurogenic bladder.

It is our opinion that in the majority of cases the patients can be treated successfully with proper immediate care and subsequent transurethral resection of the vesical neck when necessary. It should not be intimated, however, that the problem has been completely solved by any means. Each patient with a cord bladder still presents an individual problem that may require all of the ingenuity the physician may possess. There are still several basic problems which require solution. Among these problems, the following may be mentioned: (1) the therapeutic problem of the cord bladder which contains little, if any, residual urine (this type of bladder is frequently seen in children with myelodysplasia caused by spina bifida occulta); (2) the problem presented by the small group of patients with cord bladder who are unable to empty the bladder despite repeated transurethral resections of the vesical neck; (3) the problem of the irritable automatic bladder which can be made to empty completely by transurethral resection of the vesical neck but in which the intervals between evacuation of urine are too short and irregular. This type of vesical dysfunction is often aggravated by extravesical reflexes from spastic lower extremities.

PROBLEMS 1 AND 2

For some time our attention has been directed to the external urethral sphincter as a contributing factor to problems 1 and 2. For instance, in cases in which the cord bladder contains very little urine and passive

leakage of urine occurs almost continuously or active incontinence occurs frequently (problem 1), we have wondered if the external sphincter may be at fault. Cystoscopically, the appearance of the bladder (trabeculated) and of the vesical neck (usually hypertonic) is much the same as it is in any case of cord bladder in which urinary retention is present. Is there an absence of normal tonicity or flaccid paralysis of the external urethral sphincter such as is observed in skeletal muscle elsewhere in the presence of a lesion of the lower motor neuron?

In a case of cord bladder in which it is impossible for the patient to micturate or to empty the bladder completely after repeated transurethral resection of the vesical neck (problem 2), what is the nature of the impediment that holds the urine back? The only obvious obstruction left would seem to be the external urethral sphincter. Does it become hypertonic, spastic and hypertrophic and cause urinary obstruction? If the external sphincter is a factor in either of these conditions mentioned, then what is the function of this sphincter in the normal person? What is its normal state—one of neutrality, flaccidity or tonicity? Two cases in which the patients recently were treated successfully at the Mayo Clinic seem to throw considerable light on problem 1.

Case 1.—A girl, aged seventeen years, came to the clinic in September, 1945. She had been well until 1910, at which time an operation had been performed for spina bifida cystica. The patient had had no disability from this condition, but operation had been advised to avoid future troubles. After the operation, urinary retention developed and was followed later by vesical and rectal incontinence. Areas of complete anesthesia had developed in the saddle area and on the posterior aspect of the right thigh, and complete anesthesia had occurred below the right knee. This had resulted in a decubitus ulcer of the right heel, which had exposed the os calcis and had produced extensive osteomyelitis. An extensive decubitus ulcer had developed on the right buttock and had exposed the ischial tuberosity.

From the urologic standpoint, this patient was continually wet. Small spurts of urine would issue from the urethra every three to eight minutes. On several occasions, less than 50 c.c. of residual urine was found in the bladder although on one occasion 60 c.c. was obtained. Cystoscopy revealed that the bladder was moderately trabeculated and of large capacity. Because of the small amount of residual urine, it was felt that transurethral resection of the vesical neck would be of little help. We wondered, however, if the tone of the external sphincter could be improved with a muscle plicating type of operation, such as the Kelly operation, on the urethra. It was decided to try both procedures.

On October 22, 1945, transurethral resection was performed, and a total of 3 gm. of tissue was removed from the entire circumference of the vesical neck. After the operation the vesical function was not changed except that the small amount of residual urine had been eliminated. The urine still was expelled from the bladder in small spurts every three to eight minutes. A Kelly operation on the urethra was then performed. After removal of the catheter, the patient was able to void every two hours and remained dry. If awakened once at night to void, she did not wet the bed. She was able to empty the bladder completely. Sixteen months have elapsed since the operation was performed. The vesical function is still normal and the urine clear. She can initiate micturition at will.

After the urologic treatment the patient's right leg was amputated below the knee and a decubitus ulcer of the right buttock was excised. Both wounds healed well and have remained healed. The patient walks well on her artificial limb and, despite the fact that the stump is anesthetic, she has as yet had no trouble with trophic ulcers.

Case 2.—Not long after case 1 was observed, another young girl of about the same age came to the clinic because of the same type of vesical dysfunction. Her trouble had been present since birth and was due to a spina bifida occulta which had never been operated on. The same treatment was employed as in the first case, except that the Kelly operation on the urethra was done first. The procedures were reversed in this case because, although the bladder was extremely trabeculated, the urethra was not more than 1 cm. in length. After the Kelly operation was performed, the urethra was of normal length and an abnormal amount of tissue was

present at the vesical neck. This operation was complicated by delayed postoperative bleeding which is fairly common after transurethral resection on women. This necessitated repeated cystoscopy for hemostasis and resulted in a severe urinary infection which required treatment for some time.

After the successful treatment of the patients in cases 1 and 2, an attempt was made to use the same operative procedure on girls who were less than ten years of age. It was found that the vagina was too small to permit the satisfactory performance of a Kelly operation on the urethra.

At about the same time these cases were being studied we encountered a case which illustrated problem 2. The patient was a young man who had a traumatic lesion of the cord at the level of the twelfth thoracic vertebra. After multiple resections of the vesical neck, complete urinary retention persisted. The patient was finally relieved when suitable treatment was directed toward the external urethral sphincter, which apparently was spastic and causing obstruction.

Case 3—A man aged thirty years came to the clinic in January, 1946. He had been injured in an automobile accident almost two years previously. There had been a fracture of the twelfth thoracic vertebra and immediate paralysis of the lower extremities, bladder and bowels. Catheter drainage had caused a perurethral abscess. The abscess had been incised at the penoscrotal junction and a urinary fistula had resulted. Vesical calculi had developed. A suprapubic cystostomy had been performed but the opening in the bladder had been allowed to close. A urethral catheter had again been used for drainage.

When the patient came to the clinic he had the typical appearance of a paraplegic. The level of the lesion was found to be at the first lumbar vertebra. There was complete paralysis of the lower extremities aside from slight weak residual motion in the left quadriceps and adductor muscles. The abdominal muscles were normal. There was complete anesthesia of the saddle and perineal areas and over most of both legs.

Urologic examination disclosed a staghorn calculus which filled the pelvis and calices of the right kidney. There was complete urinary retention. When the bladder contained from 600 to 1,000 c.c. of urine the patient would complain of severe distress, but would be unable to pass any urine. The old urethral fistulous tract at the penoscrotal junction could be palpated but did not seem to be patent. Cystoscopy revealed a typical trabeculated hypertonic bladder with some deformity of the left wall and spasticity and contracture of the vesical neck.

In addition to the paralysis and the urinary difficulty, the patient complained of pain in the region of the gluteal muscles on the left, of some pain in the left leg and in the right leg and of occasional twinges of pain in the right renal area. It was observed that filling of the bladder or pinching the skin in the anesthetic perineal area would produce painful reflex spasm of the gluteal muscles on the left side.

Transurethral resection of the vesical neck was performed and 6 gm. of tissue was removed from the entire circumference of the vesical neck and prostatic urethra. After this procedure, the patient was still unable to micturate. The bladder would become distended and provoke recurring episodes of bleeding. Finally, a suprapubic tube was placed in his bladder and he was allowed to go home for a few months.

When he returned to the clinic, transurethral resection was performed on two more occasions and less than 5 gm. of tissue was removed at each operation. There was no more tissue that could possibly be removed. The result was essentially the same as it had been previously and the patient was still unable to void. Vesical spasm again caused repeated episodes of postoperative hemorrhage.

Attention was then directed to the external urethral sphincter. We reasoned that with the vesical neck completely resected and apparently no longer capable of being an etiologic factor, there must be some other obstruction in the urethra to account for the fact that the patient could not force urine out of the bladder with his powerful abdominal muscles. The external sphincter seemed to be the only other possible source of obstruction. In order to relax it, we produced a transsacral block with procaine hydrochloride. As soon as the anesthetic took effect, the patient could void easily with a good stream and could empty his bladder completely. As soon as the anesthesia wore off, however, the patient was again unable to void.

We then thought that the probable factor which had allowed the patient to void was the

blocking of the nerve supply of the external urethral sphincter, which possibly allowed the sphincteric muscle to relax. In an attempt to prove this, we again produced a transsacral block with procaine hydrochloride but made cysto-urethrographic studies before and during the anesthesia. We were surprised to find that the external sphincter was extremely spastic (fig. 33a) before the transsacral block was produced. During the sacral block, however, there was marked relaxation of the sphincter (fig. 33b). This information seemed to lend weight to our belief that the external sphincter was the cause of the obstruction.

There was another factor, however, which had to be eliminated before this opinion could be proved. The transsacral block should also anesthetize the pelvic nerves (nervi erigentes) which arise from the second, third and fourth sacral nerves. We could not be sure that this was not a

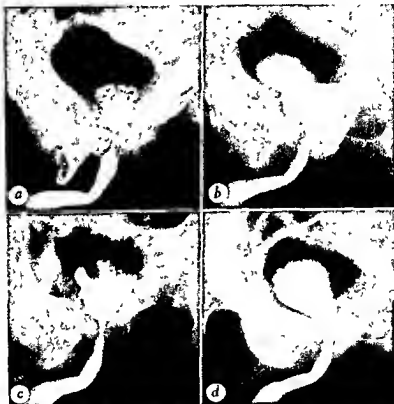


Fig. 33.—a, Cysto-urethrogram showing spasticity of external urethral sphincter in case 3. b, relaxation of external urethral sphincter during sacral block, c, relaxation of external urethral sphincter during bilateral pudendal block with procaine hydrochloride; d, relaxation of external urethral sphincter after section of the anterior and posterior roots of the fourth and fifth lumbar and the five sacral nerves.

factor in permitting the patient to void. To eliminate this possibility, we blocked the pudendal nerves with procaine hydrochloride in the area in the perineum where they emerge from Alcock's canal. Again, cysto-urethrograms were made before and during the anesthesia. The results were the same as those produced by transsacral block, that is, the patient was able to void and empty the bladder and the urethrogram (fig. 33c) again showed that the spastic external sphincter was relaxed during the anesthesia. Spinal anesthesia then was produced with procaine hydrochloride and the results were essentially the same as they had been previously, except that they were not so good as those produced with transsacral block or pudendal block.

It seemed quite clear from these studies that section of the pudendal nerves or rhizotomy of the sacral roots would relax the external sphincter and allow the patient to void. Accordingly,

section of the pudendal nerves was advised. The right nerve was sectioned first and the left nerve was sectioned a few days later. The operation was done in the perineum where the nerves emerge from Alcock's canal. Much to our surprise, this did not yield the same results as did the injection of procaine hydrochloride; therefore, we felt that some fibers had not been sectioned. It was then decided to perform an anterior rhizotomy of the sacral roots. Laminectomy was performed and the cauda equina was exposed. The roots of the sacral and coccygeal nerves (which were lying mesial to the roots of the lumbar nerves) were separated from the roots of the lumbar nerves. The anterior roots of the sacrococcygeal nerves were then separated from the posterior roots and divided between silver clips; about 0.5 cm. of the roots was removed on each side. This did not produce the desired results. The urinary retention persisted and the pain and gluteal spasm continued and caused the patient to become addicted to demerol. It was then decided to perform a complete section of the roots of the sacral nerves and possibly the roots of the last two lumbar nerves to be sure of denervating the external urethral sphincter and gluteal muscles. The lower portion of the thoracic segment of the spinal cord and the entire conus medullaris were exposed. Because of dense adhesions from the previous operation, it was impossible to separate the fibers of the cauda equina sufficiently to identify what had been severed previously. In order to sever completely all of the sacral nerves and the roots of the fourth and fifth lumbar nerves, three ligatures were passed around the entire cauda equina at the level of the third lumbar vertebra. All the anterior and posterior roots were divided below this ligature so that the roots of the fourth and fifth lumbar and the roots of the first, second, third, fourth and fifth sacral nerves were completely severed.

The result of this last procedure was excellent. The pain and gluteal spasm disappeared and the patient was able to void voluntarily with a good stream. A urethrogram (fig. 35d) showed that the external sphincter was relaxed. The patient was able to void 10 to 12 ounces of urine with a large continuous stream by using abdominal straining. At first, 150 cc. of residual urine persisted but after ten to twelve days the patient was able to empty his bladder completely. The patient was able to retain his urine and to keep dry. The only time he lost any urine was when the bladder contained more than 400 cc. If he then strained considerably (as for instance when performing his exercises in physical therapy), a few drops of urine occasionally were expelled. This could easily be controlled by not allowing the bladder to become too distended with urine or by using a penile clamp for a short time with very little compression.

Before he was ready to be dismissed, it was decided to remove the stone from the pelvis of the right kidney as it was beginning to cause pain. A right pelvolithotomy was performed. During his convalescence from this procedure, a periurethral abscess developed at the site of the original abscess and the old fistula opened and drained at the penoscrotal junction. This complicated the situation somewhat as urine ran out of the fistula when he voided. It, therefore, was difficult for him to keep dry. We have advised the patient to return in a few months for closure of this fistula if it does not close spontaneously.

The evaluation of this case is not simple. It would seem logical to assume that the obstructive factor in this case was the external urethral sphincter. On the other hand, it is not entirely clear if the hypertonicity (or the inability of the sphincter to relax) was a typical response of skeletal muscle to a lesion of the upper motor neuron or the result of stimulation from extravesical reflexes from the lower extremities and spastic gluteal muscles. It could have been from a combination of these factors. One also wonders why complete passive incontinence does not occur in a cord bladder after a combination of transurethral resection of the vesical neck and destruction of the nerve supply of the external urethral sphincter (by rhizotomy). It would seem that there must be enough urethral resistance or passive (neutral) tonicity of the external urethral sphincter to prevent incontinence of urine. In cases of autonomous bladder in which transurethral resection has produced good results, the patients can initiate micturition at will if there is a substantial amount of urine in the bladder. This is done by increasing intra-abdominal tension by setting the diaphragm and contracting the abdominal muscles (if they are intact). The patients may lose a few drops of urine if they allow the bladder to become too full and then

engage in some strenuous type of exercise. In other words, the problem is the same as urinary retention in a patient who does not have a neurologic lesion, that is, one of vesical force versus the sphincters (vesical neck and external sphincter).

CYSTO-URETHROGRAPHIC AND CLINICAL STUDY OF THE EXTERNAL SPHINCTER

In order to obtain more information about the function of the external urethral sphincter, we made a cysto-urethrographic study of five persons who did not have any neurologic lesion and of ten patients who had lesions of the spinal cord and associated vesical dysfunction.

The technic which we employed is simple; it is essentially the same as that described by Flocks and Alcock. Approximately 30 c.c. of sterile K-Y lubricating jelly is mixed with 20 c.c. of some type of radiopaque oil. This medium should be mixed just before it is to be used.

The injection of the medium is made with a 30 c.c. syringe that is attached to a piece of rubber catheter about 3 inches (7.62 cm.) long. The



Fig. 36.—Cysto-urethrogram of man who did not have a neurologic lesion; external urethral sphincter apparently in "neutral" position, *a*, before pudendal block; *b*, during pudendal block with procaine hydrochloride

patient is placed on his back on the x-ray table. One of the patient's hips is then elevated to an angle of approximately 15° and held there with a small wooden block. This position is employed to throw the shadow of the urethra away from the pelvic bones. The penis is then firmly grasped in the left hand, the short piece of urethral catheter (attached to the syringe) is introduced into the urethra and about 25 c.c. of the medium is injected slowly with firm pressure into the prostatic urethra and bladder. As the medium is being injected the first film is exposed (by using a Bucky diaphragm). A second film is exposed while the medium still is being injected.

Study of Persons Who Did Not Have Any Neurologic Lesion.—After preliminary cysto-urethrograms had been made, the pudendal nerves were blocked or transsacral block or spinal anesthesia was produced. Procaine hydrochloride was the anesthetic agent used in each instance. The bladder then was filled with fluid and in studies in which transsacral block and pudendal block were employed the subjects were helped to their feet and

observed for evidence of incontinence of urine. They then were asked to micturate. In the presence of bilateral pudendal block, all of the subjects were able to void normally; micturition could be initiated at will and there was no leakage of urine when the subjects were in various positions. In the presence of sacral block or spinal anesthesia, there was no leakage of urine



Fig. 37.—Cysto-urethrogram of man with no neurologic lesion but who had an extenstive tumor of the bladder; external urethral sphincter apparently in "neutral" position; a, before transsacral block; b, during transsacral block.



Fig. 38.—Cysto-urethrogram of man with no neurologic lesion who had extensive hypertrophy of the prostate gland; external urethral sphincter apparently in "neutral" position; a, before sacral block; b, during sacral block.

(during spinal anesthesia, the subjects were not made to stand on their feet) but the subjects were unable to initiate micturition.

Another cysto-urethrogram was made while anesthesia still was present. In each instance, the preliminary cysto-urethrogram disclosed that the urethral sphincter was in a more or less "neutral" position. The cysto-urethrograms that were made while anesthesia was present did not reveal any change in the appearance of the urethral sphincter (figs. 36, 37 and 38).

Study of Patients Who Had Lesions of the Spinal Cord.—In seven of the ten cases in which lesions of the spinal cord were associated with neurogenic vesical dysfunction, the preliminary cysto-urethrogram showed evidence of increased tonicity of the external urethral sphincter (fig. 35a).



Fig. 39.—Cysto-urethrogram showing apparent relaxation of external urethral sphincter in case of complete lesion of spinal cord.

In three cases, there was either no evidence of increased tonicity or definite evidence of relaxation or flaccidity (fig. 39). Further analysis of these cases is most interesting.

In all of the seven cases in which the cysto-urethrogram disclosed increased tonicity of the external urethral sphincter, there was evidence of

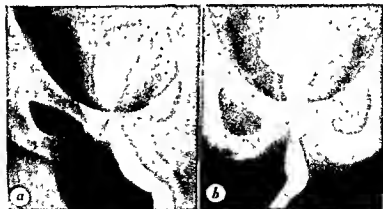


Fig. 40.—Cysto-urethrogram of typical cord bladder (automatic type) in case of complete lesion of the spinal cord, a, increased tonicity of external urethral sphincter before pudendal block; b, relaxation of external urethral sphincter during pudendal block.

varying degrees of reflex spasticity and contraction of the muscles innervated by segments of the cord below the level of the lesion (principally of the lower extremities). In two of these cases, the lesions were incomplete, they had been present for a long time; the patient had recovered suffi-

ciently to walk with crutches, but deformities of the lower extremities persisted owing to spastic contractures. The duration of the lesion was more than two years in all of these cases except one, in which it was eight months. It is interesting that this was the only case in which trabeculation of the bladder was not present. In six of the seven cases the lesion was situated between the fifth thoracic and the third lumbar vertebrae; in the remaining case, it was situated at the level of the fifth cervical vertebra. Four of the patients were studied with either one or more of the following types of anesthesia: bilateral pudendal block, transsacral block and spinal anesthesia. In all of the four cases, cysto-urethrograms made while the anesthesia was in effect showed relaxation of the spastic external urethral sphincter (fig. 40). Transurethral resection of the vesical neck was performed in all of the seven cases in which the cysto-urethrogram disclosed evidence of increased tonicity of the external sphincter. Excellent results were obtained in five of the cases (the patients were able to empty the blad-



Fig. 41—Cysto-urethrogram of typical spastic cord bladder; a, increased tonicity of external urethral sphincter before pudendal block; b, relaxation of external urethral sphincter during pudendal block.

der completely). In the other two cases, the patients were unable to void despite repeated transurethral resection but were able to void well and empty the bladder while under any one of the three types of anesthesia. One of these cases has been reported in detail above (case 3). In the other case (fig. 41) the patient refused to undergo section of the lumbosacral roots and was dismissed with an indwelling catheter.

In two of the three cases in which there was either no evidence of increased tonicity or actual relaxation of the external sphincter, the lesion of the cord had been present for a relatively short time (six to eight months) and the patients had flaccid paralysis of the lower extremities without any apparent reflex spasm. The lesions were complete in each case. In one case, it was situated at the eighth thoracic vertebra and in the other it was situated at the tenth thoracic vertebra. There was no trabeculation of the bladder in either case. Each patient could initiate micturition at will by abdominal straining with no sign of automaticity and could empty the bladder completely. In one case there was no loss of urine between voidings.

In the other case, sudden movements or straining would bring about the loss of a small amount of urine. The cysto-urethrogram in this case disclosed marked relaxation of the external urethral sphincter (fig. 39). The third case is of questionable value for this study as cysto-urethrograms were not made until after the patient had secured an excellent result from transurethral resection of the vesical neck. (The operation was done before this study was undertaken.) In this case the lesion was situated at the eighth thoracic vertebra; it had been present for six years and was complicated by complete urinary retention which had required catheterization three times daily for six years. Flaccid paralysis of the lower extremities also was present in this case and there was no evidence of reflex spastic contractures.

INTERPRETATION OF DATA

We are of the opinion that this study has plotted some new avenues of therapeutics which warrant further exploration. In the case of the cord bladder in which trabeculation, increased tonicity and urinary incontinence are present but the bladder does not contain any residual urine, the treatment must be directed toward increasing the strength of the external sphincter and weakening the vesical neck. The latter is easily accomplished by transurethral resection. The former as yet is not possible except in cases in which the patients are women and plastic operations on the urethra, such as the Kelly operation, furnish a crude but sometimes satisfactory solution of the problem.

In the occasional case in which the hypertonic external urethral sphincter is sufficiently obstructive to prevent complete evacuation of the bladder, in spite of adequate transurethral resection of the vesical neck, several surgical procedures seem to be available: (1) bilateral section of the pudendal nerves, (2) intradural section of the roots (or anterior roots only) of the fourth and fifth lumbar and the first, second, third, fourth and fifth sacral nerves and (3) the intraspinal injection of alcohol as is being used at present in some army and navy hospitals to eliminate troublesome spastic contractures of the lower extremities without resorting to rhizotomy. Section of the pudendal nerves with treatment of neurogenic vesical dysfunction has been considered previously by others interested in this subject among whom are Nesbit and Webb, and Huggins, Walker and Noonan. Experience has been insufficient to determine which would be the better procedure.

The procedure of rhizotomy again brings up the situation which we called "problem 3" in the beginning of this paper; namely, the problem of the irritable automatic bladder which has a small capacity and empties its contents completely (either with or without benefit of transurethral resection). In cases of this type, the intervals between evacuations of urine are so frequent and irregular that vesical function cannot be considered satisfactory. It has been demonstrated by Munro and other investigators that anterior rhizotomy of the lower thoracic and the lumbar nerves to eliminate troublesome massive reflexes and reflex contractions of the lower extremities often results in improvement of the automatic bladder by increasing its capacity and the time between evacuations of urine. It has been the practice, however, to preserve the integrity of the sacral roots in order to prevent the production of an autonomous (nonautomatic) bladder which is described as a type of vesical dysfunction most difficult to treat.

As stated previously, it has been our experience with transurethral resection in cases of cord bladder that the autonomous (nonautomatic) bladder responds more easily to therapy than does the automatic bladder. Furthermore, the patient can initiate micturition at will and is not bothered by having to wait for the bladder to choose its own time for evacuation. After seeing the results in case 3, we would speculate that in selected cases in which an irritable automatic bladder is associated with reflex contractions of the lower extremities a better result may be secured if the rhizotomy includes the sacral roots as well. The resulting situation should then simulate that which is present when a lesion destroys the conus medullaris and cauda equina. When such a lesion is low enough to permit preservation of the abdominal muscles, the results of transurethral resection are usually excellent. It is our opinion that this procedure should be given a fair trial.

TRANSURETHRAL RESECTION OF THE VESICAL NECK IN INFANTS AND CHILDREN*

JOHN L. EMMETT AND HENRY F. HELMHOLZ

Urinary stasis in infants and children, in which the causative lesion is below the level of the ureteropelvic junction, may often be relieved by transurethral resection of the vesical neck.

Young people who require transurethral resection may be divided into two groups: (1) those who have vesical dysfunction which results from myelodysplasia and spina bifida, and (2) those who have congenital obstruction of the vesical neck.

There are two problems to overcome in the group of patients with myelodysplasia and spina bifida: (1) relief of obstruction of the vesical neck and elimination of residual urine (which is essentially the same problem as in cases in which cord bladder results from acquired lesions of the spinal cord) and (2) correction of an incompetent external urethral sphincter. Owing to our inability to combat the latter problem, normal vesical function can be re-established in only about one in three patients of this group.

The group of patients with congenital obstruction of the vesical neck respond to treatment with transurethral resection in a much more satisfactory manner. In more than two of three patients normal vesical function can be restored. The ultimate course of these patients depends on the amount of renal damage present. Early diagnosis is therefore important. In our group of cases we did not encounter any congenital urethral valves. The type of obstruction encountered consisted of lobar hypertrophies, bars, contractures of the vesical neck, hyperplasia of the "internal sphincter" and redundant tissue at the vesical neck, and "normal appearing vesical necks."

* Abstract of paper published in full in *The Journal of Urology*. (In press.)

TRANSURETHRAL RESECTION FOR VESICAL DYSFUNCTION IN CASES OF TABES DORSALIS*

JOHN L. EMMETT AND JOHN BYRON BEARE

In 1941, we reported the results of a study of vesical dysfunction in cases of tabes dorsalis and analyzed the results of transurethral resection in thirty-five of the cases. In these cases, the results of transurethral resection were very good. We recently have made a follow-up study of these thirty-five cases and of forty-four additional cases of tabes dorsalis in which transurethral resection has been performed since December 31, 1940. These two groups of cases form the basis of the present report.

Inasmuch as minimal degrees of obstruction of the vesical neck or even a normal appearing vesical neck can be the precipitating factor in vesical dysfunction in cases of tabes dorsalis, one might logically reason that minimal degrees of postoperative scarring or contraction of the vesical neck occurring after transurethral resection could cause sufficient obstruction to produce a recurrence of the vesical dysfunction and residual urine. In such an event, it could also be assumed that transurethral removal of the postoperative scar tissue or removal of a recurring adenoma might again yield a good result. In short, we have wondered whether any of the thirty-five patients who were operated on prior to January 1, 1941, have had to undergo further treatment because of a recurrence of their former symptoms. To investigate this problem we have reviewed all of these cases. In all of these cases, more than six years have elapsed since transurethral resection first was performed at the Mayo Clinic. One of the patients has returned to the clinic for further treatment. Letters of inquiry were sent to all of the other patients and thirty-one replies were received. Follow-up data, therefore, are available in thirty-two of the thirty-five cases. In sixteen of the thirty-two cases, the patients were alive at the time of the inquiry. In nine of these sixteen cases, the letters indicated that the patients did not have any symptoms referable to the urinary bladder; there was no urinary frequency or incontinence. In six other cases, the patients reported that their vesical function was satisfactory except for the presence of varying degrees of urinary frequency and some nocturia. All of the fifteen patients felt that they were emptying their bladders completely although some stated that the urinary stream was not so large as it had been immediately after the transurethral resection. (This would indicate that these patients have had a slight degree of postoperative contracture or scarring of the vesical neck.) In the letters of inquiry, we requested the patients to have a determination of the amount of residual urine made, if possible. All of the six patients who complied with this request reported that they were emptying their bladders completely.

ANALYSIS OF FORTY-FOUR CASES OF TABES DORSALIS IN WHICH TRANSURETHRAL RESECTION WAS PERFORMED IN THE YEARS 1941 TO 1945, INCLUSIVE

We have been interested to know if our results with transurethral resection in tabetic patients will continue to be as favorable as indicated in our

* Abstract of paper published in full in the *Journal of the American Medical Association*, 135: 1093-1096 (Apr. 24) 1948.

previous report. Accordingly, we have made a study of forty-four cases of tabes dorsalis in which transurethral resection was performed at the clinic in the years 1941 to 1945, inclusive. As mentioned in our original article, we feel it is impossible to determine with any degree of accuracy in every case the proportion of the vesical dysfunction caused by the primary neurogenic atony and that produced by obstruction of the vesical neck. In most cases there was no question but that the tabetic condition was the predominating factor; in other cases, it seemed definite that the predominating factor was obstruction at the vesical neck. It is entirely possible that in a few cases the tabes dorsalis was only a coincidental finding and did not contribute to the vesical dysfunction. In the absence of an accurate method of distinguishing these conditions, it seems best to consider them as a single group.

Age and Sex.—Of the forty-four patients, forty-three were men and one was a woman. All except four were fifty or more years of age, which substantiates the thesis that most of the patients are in the age of prostatism when the vesical symptoms become sufficiently disturbing to require medical care.

TABLE I
AMOUNT OF RESIDUAL URINE BEFORE TRANSURETHRAL RESECTION
IN FORTY-FOUR CASES OF TABES DORSALIS

Residual urine, c.c.	Cases	
	Number	Percent
More than 200	8	18
100 to 200	22	50
Less than 100	14	32

Urinary Incontinence and Residual Urine.—Seventeen of the forty-four patients complained of some type of "incontinence." In six cases, the incontinence was nocturnal only and in one case it was of a precipitate urgency type. In the remaining ten cases, the urinary leakage occurred both during the day and night and varied in degree from a mild type consisting of an occasional involuntary spurt of urine to a more or less continual overflow type of dribbling from a distended bladder. In all except one case, the bladder contained more than 200 c.c. of residual urine; in twelve of the cases, more than 500 c.c. of residual urine was present. The largest amount found in any of these seventeen cases was 1,200 c.c. The amount of residual urine present in the entire group of forty-four cases is shown in table I.

Type of Obstruction of the Vesical Neck.—Consistent with our previous experience, the degree of obstruction at the vesical neck was not great. Contractures of the vesical neck, small adenomatous collars and a small degree of hypertrophy of the lateral and median lobes predominated. It should be pointed out that in many of the cases cystoscopy suggested that

the vesical neck was relaxed and dilated, and was probably not causing any obstruction. This appearance is due to the distended bladder which has pulled open and stretched the vesical neck. (The surgeon should not let this condition deter him from performing a transurethral resection, as the results of transurethral resection in this type of case are as good as in any other.) In the majority of cases, it was necessary to remove less than 10 gm. of tissue (table 2), while in only nine cases was it necessary to remove more than 20 gm. of tissue. In some cases, it was difficult to demonstrate obstruction at the vesical neck until resection actually was begun.

TABLE 2
WEIGHT AND TYPE OF TISSUE REMOVED BY TRANSURETHRAL
RESECTION IN FORTY-FOUR CASES OF TABES DORSALIS

Weight of tissue, gm.	Cases	Type of tissue		
		Adenofibrous hyperplasia	Carcinoma	Inflamed smooth muscle
0 to 3	2	1		1
4 to 5	3	4		1
6 to 10	18	17		1
11 to 20	10	10		
21 to 30	9	7	2	
Total	41	39	2	3

Results.—The results of transurethral resection were most satisfactory and essentially paralleled those obtained in our previous series. The results were classed as good in thirty-nine cases and as fair in three cases. Two patients were unimproved. By the term "good," we mean that the patient is able to void with a good stream, can empty the bladder completely, and has no urinary incontinence.

Of the seventeen patients who complained of urinary incontinence prior to operation, fifteen secured excellent results and complete relief of the incontinence. One patient, although able to empty his bladder completely, continued to have a moderate degree of urinary urgency while the remaining patient still complains of nocturnal enuresis and of difficulty in expelling his urine.

Reviewing the five cases in which the results were not entirely satisfactory, one gains the impression that further cystoscopy is indicated and that in some of the cases removal of additional tissue would improve the vesical function. In such cases, it often requires very careful observation and judgment to recognize and remove minimal amounts of tissue from the vesical neck. Removal of such tissue may make the difference between an excellent and an unsatisfactory result.

COMMENT

It is our opinion that vesical dysfunction associated with tabes dorsalis is no longer a therapeutic problem of any importance since consistently good results may be obtained by means of transurethral resection of the vesical neck. The explanation of how transurethral resection corrects vesical dysfunction in this disease seems relatively simple although it must be admitted that some points are more or less theoretic. The elimination of residual urine is brought about by weakening the vesical neck sufficiently to permit the weakened atonic bladder, aided by intra-abdominal and, if necessary, manual compression, to expel the urine completely. The elimination of the residual urine also relieves the incontinence in cases in which the patients are suffering from an overflow type of incontinence. The explanation of the relief of incontinence that is principally an involuntary type of micturition also seems fairly simple. The elimination of residual urine increases the reservoir capacity of the bladder. The patient is instructed to micturate regularly every three or four hours to prevent undue distention of the bladder so that the chance of involuntary micturition is minimized. He is instructed to take the time and make the effort to empty his bladder completely at each micturition. In some cases in which advanced sensory damage is present, the patients never may regain the desire to micturate. Such patients must be carefully taught to micturate at regular intervals and not to wait for the desire to micturate. Inasmuch as the bladder is emptied completely at each voiding, the urine may be kept free of infection; therefore, for all practical purposes, the vesical function may be considered normal.

One word of caution should be given. Inasmuch as small degrees of obstruction of the vesical neck can precipitate vesical dysfunction in cases of tabes dorsalis, small degrees of postoperative contracture may conceivably cause a recurrence of the obstruction. Because of this, such patients should be re-examined at yearly intervals to determine if any residual urine is present. If it is, cystoscopic re-examination of the vesical neck should be performed and any scar tissue should be excised.

TRANSURETHRAL PROSTATIC RESECTION IN CASES OF BLOOD DYSCRASIAS*

LAURENCE F. GREENE AND FRANK J. HECK

Forty patients with various types of blood dyscrasias underwent transurethral prostatic resection. The majority of these patients had pernicious anemia but patients with chronic myelogenous leukemia, chronic lymphatic leukemia, hemophilia, polycythemia vera and hemolytic icterus are included. The fact that no patient died after the surgical procedure indicates that the surgical risk is not high when proper treatment is provided during

* Abstract of paper published in full in *The Journal of Urology*, 60:247-253 (Aug) 1948.

the preoperative and postoperative periods. The important factors of treatment for each type of dyscrasia are described in the complete paper. With the exception of hemophilia the postoperative convalescence of this group of patients is similar to that of patients without blood dyscrasias and the functional results of the operation are equally as good.

In every case examination of the prostatic tissue removed at operation disclosed benign adenofibromatous hyperplasia. In one case of chronic lymphatic leukemia, dense lymphocytic infiltration was present. It is a singular fact that not one instance of prostatic carcinoma was encountered, inasmuch as one would normally expect to find six to eight cases of carcinoma in a group of this nature.

PRIMARY CARCINOMA OF THE MALE URETHRA*

JERRY ZASLOW AND JAMES T. PRIESTLEY

Fortunately, primary carcinoma of the male urethra is a relatively uncommon lesion. In 1939 Kreutzmann and Colloff reviewed the literature, collected data on 148 cases reported to that time and added two of their own. In 44 per cent of these cases the lesion was in the penile portion of the urethra and in the remainder it was located in the bulbomembranous

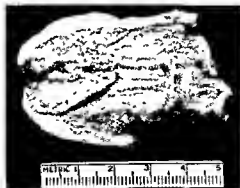


Fig. 42.—Epithelioma arising in anterior tip of urethra in a white man aged seventy-four years.

or prostatic urethra. In 1945 Perez Castro collected data on twenty-eight cases from the literature in which the growth was confined to the region of the fossa navicularis and reported one case from his personal experience. A recent review of the literature revealed thirty-three cases in addition to those reported by Kreutzmann and Colloff. Of these additional cases, in five not mentioned by Perez Castro the lesion was reported as arising in the fossa navicularis.

The present report was stimulated by a white man seventy-four years

* From *The Journal of Urology*, 58, 207-211 (Sept.) 1947.

of age who presented an epithelioma, grade 2 (Broders' method), situated in the fossa uavicularis and for which a partial amputation of the penis was performed (figs 42 and 43). Inasmuch as there have been few reports in the literature during recent years of any appreciable number of cases of this type, it seemed worth while to review the records at the Mayo Clinic for the purpose of making a clinical study of these lesions. In this review it was found that twenty-five cases of primary urethral neoplasm have been encountered from 1910 to 1945, inclusive. The diagnosis was established

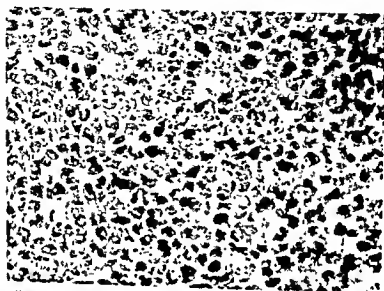


Fig 43 -- Microscopic view of gross specimen shown in figure 42 ($\times 350$).

by microscopic examination in all but three of these cases. In all cases studied histologically the diagnosis was epithelioma. Presumably an adenocarcinoma of the glands of Littre might be classified as a urethral neoplasm but no such lesion has been encountered. Cases of adenocarcinoma in the posterior urethra have not been included, as it is virtually impossible to prove that such lesions do not originate in the prostate or other glandular structures.

CLINICAL CHARACTERISTICS

The classification offered by Kreutzmann and Colloff is practical and useful in discussing urethral carcinoma. These authors considered all growths in the penile urethra as "anterior" and all others as "posterior." From a therapeutic point of view, treatment frequently varies depending on the location of the lesion. In the present series of cases the growth was situated anteriorly in ten cases and posteriorly in fourteen, and in one case both the anterior and posterior urethra were involved, a proportion in accord with reports in the literature. So far as symptoms and clinical characteristics are concerned there was little difference regardless of the location of the growth, however, the most common initial symptom for an anterior lesion was difficulty in micturition, whereas for a posterior lesion hematuria was most often the presenting symptom. If a growth is of appreciable size

it can be palpated, especially if it is located in the anterior urethra. Six of the twenty-five patients presented a history of urethral stricture prior to the onset of symptoms referable to the neoplasm, an incidence which seems somewhat more than coincidental. The average age of patients was fifty-six years and the youngest was only twenty-eight years of age. The grade of malignancy was determined in twenty cases and in nineteen was either 2 or 3.

TREATMENT

In the present series of cases treatment varied depending on the location and extent of the lesion. In the ten cases in which the growth was located in the penile urethra, amputation, radium and fulguration were employed with equal frequency. Amputation, which may be partial rather than complete, is preferable for the more extensive lesions. It is well to remember, however, that a partial amputation which leaves virtually no urethra which may be grasped during micturition to direct the stream may be more of a handicap to the patient than a perineal urethral meatus which can always be used satisfactorily in the sitting position. For a relatively small growth in the region of the fossa navicularis, radium may be applied directly. Fulguration can be used to destroy a relatively small lesion. If there is any question about the complete destruction of the growth in situ by either of these methods, amputation would seem the treatment of choice.

Treatment of an epithelioma situated in the membranous or prostatic urethra is somewhat more difficult. In the present series of cases, prostatectomy, cauterization, application of radium, transurethral removal and fulguration and roentgen therapy were employed. Obviously there must be individualization in the choice of treatment, depending on the exact location and extent of the lesion. Experience has been too limited to permit general conclusions but obviously the same principles apply in the treatment of a malignant lesion in the posterior urethra as in other parts of the body; namely, complete removal or destruction of the growth if at all possible.

RESULTS

The number of cases in this group is entirely too small to permit significant opinions regarding results and the efficacy of various types of treatment. From a study of these results, however, certain impressions are gained which are in accord with reports in the literature. Thus, the prognosis in our cases seems more favorable for lesions in the anterior than in the posterior urethra. Since at least half the patients with anterior urethral lesions are living two years after operation, while half those with posterior urethral lesions are dead one year after operation, probably the difficulty of complete removal of a growth situated posteriorly may be a factor in this regard. Of the ten patients who had an epithelioma in the anterior urethra three are known to be dead and seven are living. Three of these seven have had a recurrence and none of them is known to have survived for as long as five years. The shortest postoperative follow-up in this group of seven patients was five months and the longest five years, the average being twenty-one months.

Of the fourteen patients who had lesions in the posterior urethra twelve are known to be dead; however, one of these lived four years and another

nine years and at the time of death had no evidence of recurrence. One other of the fourteen patients was alive and apparently well at least five years after treatment and one patient has not been traced. The patient who had a lesion which involved both the anterior and posterior portions of the urethra died four months after treatment, which consisted solely of roentgen therapy. Obviously, the results of both groups of cases leave much to be desired. However, the fact that a few patients have survived as long as five years affords some encouragement. For the most part treatment in these cases consisted in complete surgical removal or local destruction of the lesion.

COMMENT

The role that urethral stricture plays as an etiologic factor in carcinoma of the urethra is questionable. The incidence of this condition prior to development of the malignant lesion, as reported in the literature, seems as though it might be significant, although the majority of patients who have epithelioma of the urethra probably have no antecedent history of stricture.

The prognosis for malignant lesions of the urethra is impossible to determine from the literature, as too few cases have been reported five or more years following treatment. In general a growth situated in the anterior urethra appears to have a somewhat better prognosis than one situated posteriorly. In our experience this cannot be explained by any difference in time at which these patients presented themselves for treatment, as the duration of symptoms prior to therapy was the same for both groups of patients. It is stated in the literature that lesions in the posterior urethra are recognized later than those in the anterior urethra. The most common symptoms for both groups were hematuria, penile discharge and dysuria. From the meager data available the grade of the lesion has not affected the prognosis significantly.

Not included in the present series of cases are a few in which small epitheliomas developed in the urethra subsequent to total cystectomy for carcinoma of the bladder. While an occurrence of this type is not especially frequent, it is encountered sufficiently often that it should be kept in mind. Particularly if the growth in the bladder involved the region of the vesical neck, follow-up examination should include endoscopic inspection of the remaining portion of the urethra. Recurrences of this type may then be recognized while they are quite small and may be adequately controlled by fulguration. In two cases repeated fulguration of this type has been required over a period of several years. As mentioned, however, these cases have not been included in the present study because they are not thought to represent true primary lesions in the urethra.

CLINICAL SIGNIFICANCE OF GROSS HEMATURIA*

LAURENCE F. GREENE

Gross hematuria may be produced by a host of medical diseases such as hemorrhagic nephritis, hemophilia and acute leukemia, but a discussion of these conditions is not germane. Of the urologic causes of gross hematuria, malignant lesions and infections of the urinary tract lead the list; these are followed by urinary calculi and prostatism.

The age of the patient is important. Gross hematuria is rare during infancy and childhood. When it occurs, it usually is in response to infection, which usually is the result of congenital obstruction in some part of the urinary tract.

In young adults and persons up to the age of forty, gross hematuria is most commonly a manifestation of infection in the form of pyelonephritis or cystitis. The infection is most commonly produced by organisms belonging to the colon-typhoid or staphylococci groups; tuberculous infections are also common in this age group. Gross hematuria associated with renal or ureteral colic is not uncommon in the presence of renal or ureteral calculi.

After the age of forty years, gross hematuria as a result of neoplasms of the kidney, ureter or bladder becomes more frequent. In men of this age group, prostatism, both benign and malignant, is a common cause of hematuria; furthermore, the incidence of gross hematuria is greater in benign prostatic hyperplasia than in prostatic carcinoma. Infection, both specific and nonspecific, and urinary calculi are less common causes of gross hematuria in this age group.

A detailed description of the nature of the hematuria may help. In males it should be determined whether the hematuria is initial, terminal, total or independent of micturition. Initial hematuria is characterized by the appearance of blood only at the start of micturition; during the act the urine becomes clear. Initial hematuria is usually produced by prostatism or lesions in the prostatic urethra. In such conditions, blood or blood clots accumulate in the prostatic urethra; when urination is initiated the initial urine is bloody and the remainder clear. In terminal hematuria, clear urine is passed until termination of the act, when the urine becomes bloody. Terminal hematuria may result from prostatism or lesions in the prostatic urethra; in such instances, the sudden contraction of the accessory muscles of micturition is responsible for the terminal hematuria. Rarely vesical neoplasms may be traumatized by the contraction of the bladder and produce terminal hematuria. In total hematuria the urine appears bloody throughout micturition. Total hematuria is usually produced by lesions of the kidney and ureter. The blood enters the bladder and becomes well mixed with the urine. Lesions in the bladder likewise may result in total hematuria. Rarely lesions of the prostatic urethra will bleed into the bladder and result in total hematuria. Bleeding independent of micturition is produced by lesions situated external to the external sphincter.

The color of the hematuria may be of some help in diagnosis. Dark brown urine usually results from bleeding lesions in the upper part of the

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urinary tract whereas bright red urine is usually associated with lesions in the lower part of the urinary tract. It may be extremely difficult to determine whether bleeding arises from the urinary or genital tract in females; however, careful catheterization and examination of the urine will usually settle the question.

Particular attention should be paid to certain phases of the physical examination of a patient who complains of gross hematuria. Renal enlargement due to neoplasm, hydronephrosis, cyst or polycystic kidney may be detected. Tenderness in the flank, a result of infection, may be elicited. Careful palpation of the supraclavicular area should be carried out because hypernephroma may metastasize to the lymph nodes at that site. The appearance of a left varicocele late in life is suggestive of a neoplasm of the left kidney. This condition is the result of the anatomic relations of the left spermatic vein. Neoplasms of the kidney tend to invade and block the renal vein. Inasmuch as the left spermatic vein empties into the left renal vein, the blockage of the latter vein is transmitted to the spermatic vein and results in varicocele. If the neoplasm invades the inferior vena cava, dilated abdominal veins may be visible.

The suprapubic area should be examined carefully in order to detect the presence of a distended bladder, tenderness that may accompany cystitis or a mass due to a vesical neoplasm. By means of a careful rectal examination of a man, a diagnosis of benign prostatic hyperplasia or prostatic carcinoma may be made. By rectal palpation it may be impossible to distinguish prostatic carcinoma from tuberculous prostatitis or prostatic calculi and other diagnostic aids may be necessary. Infiltration of the base of the bladder by vesical neoplasm may be readily detected by rectal palpation.

In cases in which the patients are females, considerable information may be obtained by vaginal examination. In this manner, infiltration caused by vesical neoplasm and tenderness caused by cystitis may be detected. It may even be possible to palpate a calculus low in the ureter by vaginal examination.

Examination of the external genitalia may aid in the diagnosis. The presence of urinary tuberculosis may be suggested by noting evidences of genital tuberculosis inasmuch as these two conditions are frequently concomitant. Tuberculosis of the vas deferens and epididymis usually results in enlargement, hardening and nodularity of these organs. A urethral neoplasm may be palpable along the course of the urethra.

Hematuria is rarely an emergency unless it is prolonged and exsanguinating in character. Until the time when the patient can be placed in proper hands, there are several steps that may be taken. If it is suspected that the bleeding arises from the kidney or ureter, the patient should be put to rest in bed and necessary narcotics given to relieve pain. A large fluid intake should be urged to prevent the formation of clots and subsequent "clot colic." If the bleeding is vesical or prostatic in origin and associated with the formation of clots, an effort should be made to remove the clots. The presence of clots in the bladder acts as a foreign body and produces vesical spasms which aggravate the bleeding. The clots may best be removed by a urethral catheter and syringe.

ETIOLOGY, PREVENTION AND TREATMENT OF VESICOVAGINAL FISTULA*

VIRGIL S. COUNSELLER

The management of vesicovaginal fistula has been somewhat simplified during the past decade. The incidence of postoperative recurrences has been greatly reduced, so that they now occur only in the most difficult cases.

ETIOLOGY AND PREVENTION

Vesicovaginal fistula is caused by difficult parturition and operations on the uterus and bladder; occasionally it follows the application of radium for cancer of the uterine cervix.

The fistula which occurs after delivery used to be the most commonly seen, now such a fistula is rarely seen at the clinic. The type of vesicovaginal fistula we see today is chiefly that which occurs postoperatively. The operation which is most usually involved is total abdominal hysterectomy; the next in order of frequency are vaginal hysterectomy and vaginal plastic operations. The fistula which develops from radiation therapy for carcinoma of the cervix is not common, but when it is seen it presents a serious surgical problem.

Since the frequency of occurrence of vesicovaginal fistula which follows abdominal hysterectomy is increasing, greater effort must be made to prevent such a surgical accident. One reason for this increase has been the great number of papers published in which total abdominal hysterectomy is advocated as a routine procedure whenever abdominal hysterectomy is indicated. I am not in accord with such teaching because it is not practical to apply one surgical procedure to an organ such as the uterus with no regard for the type or location of the inherent lesion. Total hysterectomy can be done successfully by a competent surgeon, but not by one with less ability without an increased risk.

It seems to me that the usual manner in which a vesicovaginal fistula develops after total abdominal hysterectomy is as follows. It is possible for a surgeon to incise the bladder without knowing that he has done so, particularly if the bladder has been emptied by catheter preceding the operation. Second, and what I believe is the most common cause, is the placing of a suture through the wall of the bladder when the vaginal vault is being closed. Also, when a stick tie is being placed to ligate the uterine vessels, the bladder may be caught near the ureterovesical juncture and vesicovaginal fistula develop therefrom. Such a fistula becomes apparent within about a week after the operation. This period is the amount of time required for the suture to cut through the wall of the bladder. If the fistula occurs immediately after the operation, it must certainly be the result of an unrecognized injury of the bladder. Such injuries can be prevented by certain maneuvers which I wish to recommend, since I feel that prevention is fully as important as cure in the treatment of this condition.

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To avoid the production of vesicovaginal fistula after total abdominal hysterectomy, the operation should be done under direct vision, without the causing of trauma or hemorrhage. If every step of the operation is conducted under direct vision, and no structure is incised or sutured except when it is plainly seen and identified, then a fistula will not be caused. It is especially important that after the peritoneum has been incised and pushed down from the uterus, the bladder be pushed downward at least 1.5 cm. to expose that much of the attachment of the pubocervical fascia at the point of its attachment to the cervix. It is only after this maneuver that the clamps can be placed safely on the uterine vessels and the cervical branches of the uterine artery without the risk of catching a tiny segment of the bladder in the tips of the forceps. Catching of a small portion of the bladder in the forceps is more likely to occur in the presence of very active bleeding from some of the larger veins of the broad ligament. For this one reason alone, I feel that it is a good routine procedure, in the performance of abdominal hysterectomy, to cut the round ligament separately from the adnexal ligament. If this is done, exposure of the vessels of the broad ligaments will be adequate, so that the clamps can be applied effectively in the proper places.

In cases in which there are interligamentous fibroids, adenomatous lesions, pelvic endometriosis or chronic pelvic cellulitis, the normal anatomic relationships or positions of the vessels and the ureteropelvic segment of the wall of the bladder may be markedly distorted. Therefore, greater caution must be observed in the conduct of total hysterectomy in these situations if subsequent trauma to the bladder and the development of a vesicovaginal fistula are to be avoided.

There is a step in the technic of total abdominal hysterectomy which I have observed to be important as an aid to visualization of the structures and also as a means of assistance in the prevention of serious hemorrhage. This consists in the surgeon's holding the pelvic structures to be removed by one hand and his maintaining constant traction on them, because under moderate traction the anatomic aspects of these structures are more clearly defined and hemorrhage from veins which may be torn cannot be excessive. In this connection, I wish to advise against the use of right-angle clamps or any type of clamp which may be used to close the vagina after complete removal of the uterus. The risk of injury to the bladder is too great when such clamps are employed, whereas the risk of serious infection presented by the open vagina is very small indeed.

A fistula which follows vaginal hysterectomy without doubt is produced in exactly the same manner as is that which follows abdominal hysterectomy. The same principles, therefore, of direct vision and hemostasis which I have just mentioned are most important in the prevention of this type of fistula after either vaginal hysterectomy or vaginal plastic procedures carried out for cystocele decensus and amputation of the cervix.

The prevention of vesicovaginal fistula after radiation for carcinoma of the cervix is a problem for the radiologist. As long as this treatment remains in the hands of an expert radiologist, the occurrence of this type of fistula will be held to a small figure. Radium is a very powerful element and cancer of the cervix is a very serious disease, so that expert care in handling both must be used.

UROLOGIC INVESTIGATION

When a patient presents herself with a vesicovaginal fistula, the first steps of investigation are urologic. It must be determined whether one fistula is present or several are present. The exact situation and size of the lesion, presence or absence of cystitis, and involvement or noninvolvement of the upper part of the urinary tract must be ascertained.

One of the most common sites at which a vesicovaginal fistula occurs is just above or parallel to the ureterovesical junction as a result of injuries which have been produced by the forceps or stick tie in clamping and ligating the uterine vessels during abdominal hysterectomy. Because of the proximity of such a fistula to the ureter, special care must be used during repair to prevent ureteral obstruction and recurrence of the fistula. When a fistula is situated in or near the ureteral meatus, the urologist must make a careful survey of this area and the upper part of the urinary tract.

So far as situation is concerned, those fistulas which are located in the midportion of the trigone or posterior to the trigone usually are uncomplicated and single, and the upper part of the urinary tract is normal. When the fistula involves the sphincter the problem of repair becomes somewhat more complicated, so that, in order to secure the best results, accurate specification as to location of the fistula on cystoscopic examination is essential.

The appearance of a fistula which has been produced by radium is characteristic in that the mucosa appears lighter and is scarred for a variable distance around the fistula. This scarring is caused by loss of the blood supply, and will not heal well if it is repaired. Hence, if repair is to be considered, this entire area, which previously has been described on cystoscopic examination, must be excised.

A fistula located anterior to the sphincter becomes a urethro vaginal fistula, but on vaginal examination it may appear to be a vesicovaginal fistula. Localization in such a case is important so far as repair is concerned, since tissues suitable for repair are scanty around the urethra, in contrast to those at the base of the bladder.

Infection in the bladder, which used to be a serious complicating factor, has now been reduced by the use of sulfonamide drugs and penicillin. Formerly, incrustated cystitis was a common observation in association with some of the larger fistulas because of the presence of urea-splitting organisms. Also, these infections were very potent causes of recurrences because the site of repair became infected and broke down. I find it worth while now to carry out these repairs when the urine has been made slightly acid or neutral by maintenance of the pH of the urine at about 5 or 5.5. This concentration is to be watched closely during convalescence of the patient, to prevent infection.

SURGICAL REPAIR

Before the attempt is made to repair any vesicovaginal fistula, the question of a vaginal, transvesical or transperitoneal approach to the fistula must be considered. At the Mayo Clinic the attitude toward these various methods can be expressed best by the statement that 99 per cent of all vesicovaginal fistulas in our hospitals are repaired by the vaginal approach. I shall try to state clearly our reasons for this attitude. Mobilization and

excision of scar tissue are two procedures of utmost importance to successful closure, and they are more easily accomplished by way of the vagina. The entire urethra, trigone and base of the bladder can be exposed by the vaginal approach. If the fistula followed delivery, repair of a cystocele or a urethral diverticulum, or if it developed after supracervical hysterectomy, adequate exposure and method of approach are best obtained with the patient in the lithotomy position. However, if a fistula has occurred after total removal of the uterus, either vaginally or abdominally, mobilization and excision of scar tissue can be accomplished best vaginally, with the patient in the Kraske position, which is in reality a modified Sims' position (knee-chest). Exposure, which is so essential, is excellent when this position is employed. The vaginal vault, which usually is movable, falls forward and the fistula can be seen easily, just as Marion Sims stated in his original contributions. A Sims speculum is held against the perineum, and the line of closure of the vaginal vault after hysterectomy is easily located and palpated. Generally, the fistula is situated in this area. In mobilizing the bladder, the surgeon should incise the vaginal wall well above the fistula, well below it and about 1 cm. around the fistula. The vaginal wall is reflected from the bladder at least 2 to 2.5 cm. That part of the vaginal wall adjacent to the fistula is held by forceps or clamps. The cul-de-sac of Douglas is then opened so that the surgeon's finger can explore the pelvic cavity to separate any portion of the small bowel or sigmoid from the bladder. The bladder can then be pulled more into the vagina, and all scar tissue around the fistula can be excised easily under direct vision of the surgeon.

The defect in the bladder is closed in layers either anteroposteriorly, transversely or diagonally, depending on which direction the course of the fistula is found to have after the scar tissue has been removed.

The technic of closure and the suture material to be used seem to me to have an important effect on the success of the operation. I recommend that absorbable suture material be used throughout, so that there will be no sutures to be removed secondarily. The first row of sutures is made with 000 chromic catgut. This suture brings only the mucosa together and does not enter the bladder; it is a continuous stitch. The wall of the bladder is now closed in layers. The second row of sutures is made with 00 chromic catgut; it begins 1 cm. beyond the first row and extends 1 cm. beyond the point at which the first stitch ends. The third row of sutures is made with 0 chromic catgut; this row completes closure of the bladder by starting and ending 1 cm. beyond the second row. The third row is so placed that all dead space along the site of repair of the wall of the bladder is completely obliterated. The final step is closure of the vaginal wall with interrupted number 1 chromic catgut suture material. The vaginal wall is always incised around the fistula anteroposteriorly, even though the defect in the bladder may have to be repaired transversely.

The type of repair described in the foregoing paragraph has been highly successful. I wish to recommend it. Obviously, this type of operation cannot be done transvesically or transperitoneally. I do not wish to say that such a fistula cannot be repaired by these other methods, for it can be so repaired. Occasionally, in fact, the transvesical or transperitoneal type of operation is definitely indicated, as, for instance, when a fistula is situated

high in the vault, fixed and involved with the colon. In such an instance, however, the risk is much higher and the operation is more difficult than would be true otherwise. If the fistula fails to heal, the result usually is an extra fistula situated above as well as the one in the vagina, and a much sicker patient.

Should a recurrence develop, repair ought not to be attempted for three to six months later. Such a period is approximately the time required for all inflammation and edema to disappear and for an adequate blood supply to return to the tissues. Occasionally, if a small leak follows what seems to be an adequate repair, the fistula will close spontaneously during the healing process if a catheter is kept in the bladder. Also, tiny openings may be closed later by very light fulguration and the use of an indwelling catheter.

Repair of a fistula subsequent to radiation therapy for carcinoma of the cervix should not be attempted for at least three years, for this is the minimal period in which the surgeon can be reasonably sure that there will not be a recurrence of the carcinoma. In most instances it will be wiser to transplant the ureters to the sigmoid in one stage, after careful preparation of the bowel. The oral administration of succinylsulfathiazole and the hypodermic administration of streptomycin reduce the bacteria in the colon, so that the risk of transplantation now is much safer than it was formerly.

POSTOPERATIVE CARE

Finally, I wish to emphasize the importance of postoperative care. The patient remains on a Bradford frame suspended about 2 feet from the surface of the bed for two weeks. The catheter drains directly into a small basin on the bed, so that the patient or any attendant can see at a glance whether or not the catheter is functioning. The catheter is irrigated frequently to prevent plugging, and the bacterial content of the urine is controlled by the use of sulfonamide drugs and mandelic acid.

Postoperative examinations of the vagina are not permitted until one week after dismissal of the patient from the hospital, since there is nothing to be gained by such examinations, and they may do much harm if healing is delayed.

OVARIAN DYSFUNCTION IN YOUNG WOMEN TREATED WITH LOW-DOSAGE IRRADIATION*

DELLA G. DRIPS

Before 1927 at the Mayo Clinic when a young woman confronted us with the problem of functional menstrual irregularity, we could only advise that she maintain her weight at what was normal for her on a well-balanced diet, get plenty of out-of-door exercise and avoid nervous tension. In addition to such general measures, if we found the basal metabolic rate

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to be lower than normal we would suggest raising the rate to around -3 per cent by administration of thyroid extract and maintaining it at this level for several months hoping to correct the menstrual disturbance. Sometimes ovarian extracts were prescribed with little hope of success.

About 1925 there began appearing in the German literature reports of the use of roentgen rays over the ovaries in the treatment of the functional menstrual disturbances with benefit. In cases of amenorrhea, the menses had been re-established. Rubin in New York soon reported similar results. It was decided to try this treatment at the clinic. We used extreme caution at first, irradiating only one ovary according to the technic of Rubin.

Our good fortune in establishing regular menses in the patient treated encouraged us to continue to use low-dosage irradiation. It has proved the most dependable means of re-establishing the menses after a period of amenorrhea and of continuing the menses regularly for a few months, a sufficient time to allow the patient to become pregnant.

STUDY OF 331 CASES

We have reviewed the histories of 430 cases of typical functional menstrual irregularities treated here at the clinic during the years 1927 to 1941. Ninety-nine cases are not included in this study. A small group was omitted because the patients had some systemic disease (diabetes, rheumatoid arthritis or tuberculosis) which, though it seemed well controlled at the time of the treatment, had no doubt been a factor in the initiation of the amenorrhea. The others were left out because the follow-up information was either not obtainable or was unsatisfactory, or because they were more than thirty-two years of age. I wished in this study to include only the younger women. This left 331 cases.

It seemed advisable to separate the patients treated primarily for amenorrhea into two groups, those single and those married at the time of treatment. Among the married women, we were interested especially in the direct effect of irradiation on the sterility associated with ovarian dysfunction. As is well known, a high percentage of these women are sterile. We wished to determine whether treatment was worth while when the amenorrhea had been present for more than one year so the cases of amenorrhea were subdivided again into those in which the period of amenorrhea was less than a year and those in which the period of amenorrhea was more than a year.

In the whole group of single women treated with irradiation from 1927 to 1941, inclusive, for an ovarian dysfunction of the amenorrheic type there were 136 in all. In sixty-three of these, the dysfunction was considered to be primary in the pituitary and in seventy-three primary in the ovaries.

In forty-six (73 per cent) of the group of sixty-three cases of pituitary failure, regular menses were re-established directly after treatment. Two patients had only temporary improvement. In the other cases the improvement continued for more than one year. The dysfunction of nine young women did not improve after the irradiation therapy but later on the menses returned spontaneously.

In forty-eight or 66 per cent of the group of seventy-three cases in which the menstrual irregularity was considered to be due to primary ovarian failure, regular menses were re-established. In seven only temporary im-

provement was achieved. In the others menstruation continued to be regular for one year at least. Fourteen young women who received no benefit from irradiation began to menstruate later, spontaneously.

When the period of amenorrhea was more than one year, in only about 14 per cent of the cases of primary ovarian failure was improvement noted and this lasted only three months in four cases in which irradiation only was used. In the cases of amenorrhea due to pituitary failure that had been present for more than one year improvement was noted in about 62 per cent and temporary improvement occurred in fewer cases. This makes it evident that the sooner young women who have amenorrhea are treated the better the chance of re-establishing and continuing the menses.

To a group of the young women treated for menstrual irregularity while single from 1930 to 1941, questionnaires were sent out in 1945. We asked them simple questions relative to their general health, the regularity of their menses, whether they had married, if they had been pregnant and, if so, how many children they had had. Fifty-five answered the questions intelligently. Twenty-one women were still single. Twelve of these women stated that menstruation had become more regular after treatment; fourteen stated their periods were regular, seven related that their periods were still irregular, and three of these who were amenorrheic when treated had not had any period since treatment. Thirty-four women had married. Twenty-four of these stated their menses had become more regular after treatment; twenty-six reported that they were having regular periods in 1945; twenty-five women had been pregnant and had had forty pregnancies. Two of these had ended in miscarriages. One patient gave birth to a monster. This long range study of low-dosage irradiation in young women makes us feel that there is no late harmful effect on the ovaries.

As I have stated, the goal to be approached in treatment of young married women complaining of menstrual irregularity and sterility is the establishment of regular periods until pregnancy can take place. It was assumed by all these women that they were responsible for the sterility. In most of the cases the husband was not with the patient when she was at the clinic and we have no way of knowing which was sterile. This study would be more valuable if this were known. Any young married woman who has abnormal menses and is childless feels sure she is to blame for the sterility and usually will go to any length to correct it. In the results of this study pregnancy has been considered to have been made possible by treatment if the patient became pregnant within three months after regular menses were established. *Subsequent pregnancies have not been counted.*

Of one group of sixty-two women who were married when treated, we have sufficient clinical records (over several years in the majority of cases) so that a questionnaire in 1945 was not deemed necessary. Forty-two of the women were improved with treatment and thirty-six continued to have regular periods; nineteen became pregnant directly after treatment and three of these pregnancies were terminated early in abortion. One woman in this group had three roentgen-ray treatments over a period of years and pregnancy directly followed each treatment.

A second group of sixty-one women who were married when treated from 1927 to 1940, inclusive, were sent questionnaires in 1945 and reported as follows: Forty stated their menstrual periods had become more regular

after treatment, thirty-nine and their periods were regular in 1945. Twenty-six had been pregnant; fifteen became pregnant directly after the treatment. Two pregnancies had terminated in abortion and one woman had had a tubal pregnancy. To 1945 the twenty-six women who became pregnant had had forty-six full-term pregnancies, five miscarriages and two tubal pregnancies.

In summary, of 123 young married women treated with low-dosage irradiation thirty-four (27.6 per cent) had become pregnant directly after treatment. Eighty-two women stated their menstrual periods were definitely more regular after treatment and of these forty-five had been pregnant and had had sixty-seven full-term pregnancies, ten abortions and two ectopic pregnancies; one patient gave birth to a monster after a full-term pregnancy.

Low-dosage irradiation for dysmenorrhea with regular, normal menses was given to twenty-four women; eighteen were improved for six months and eight for at least two years. One young woman became pregnant directly after the treatment. None of these young women complained of any menstrual irregularity after treatment. Several requested repetition of the treatment which had given relief several times. The effect would usually last about six months and then treatment would have to be repeated. Fearing this repetition of treatments we stopped advising it.

Twenty-two women who had regular, normal menses and were sterile and whose husbands' fertility had been checked and found within normal limits by the criteria used previous to the last five years (no morphologic study) were given low-dosage irradiation over the pituitary and ovaries. Eleven received pregnancy serum in addition to irradiation and five others were given estrogen and progesterone in addition. Three became pregnant but only two pregnancies occurred directly after treatment. Six women complained of irregularity of periods after treatment. These were the only patients of the whole group treated with irradiation who made complaints about the treatment.

It does not seem wise to treat women for sterility alone with low-dosage irradiation. The sterility in these cases apparently is not dependent on ovarian dysfunction.

COMMENT

In treatment of functional menstrual irregularities, the object is to try to establish more regular normal menses and continue these until pregnancy can take place. Pregnancy is often a stimulus to the endocrine glands involved and the menses may continue normally thereafter though this is not by any means always the case. One hopes with treatment also to relieve symptoms associated with the abnormal menstruation.

Of the two groups of patients who have the amenorrheic type of menstrual irregularity, the group in which pituitary failure is considered to be responsible responds best to treatment unless the atrophy of the genital tract has become irreversible. The best results are attained when amenorrhea has been present for less than six months and for this reason treatment should be begun early.

In cases of the exogenous type of pituitary failure, general hygienic measures, administration of thyroid extract and cyclic administration of estrogens or of estrogens and progesterone are usually sufficient to bring about return of the menses.

In the endogenous type and in any pituitary failure when the period of amenorrhea has been more than a year such treatment is often not sufficient to bring about return of the menses and low-dosage irradiation over the pituitary and ovaries is resorted to. It is best to establish a normal basal metabolic rate by administration of thyroid extract and to try cyclic administration of ovarian hormones (principally estrogens) for several months before giving irradiation. Frequently also though the menses may have become fairly well regulated by administration of thyroid extract and estrogen the married woman does not become pregnant and, provided her husband's fertility is normal, stimulation of the pituitary and ovaries by means of irradiation may bring about pregnancy immediately or at least in a few months after treatment. It is most essential in such cases that administration of thyroid extract and estrogen be continued through the pregnancy; if this is not done early abortion may occur for when ovarian dysfunction has been the rule and pregnancy has occurred early abortion is a common sequence. In recent years, since potent estrogens have been available for oral administration some women who formerly have aborted several times have carried through a pregnancy with this therapy. In our cases in which we used irradiation before we had potent estrogens, we did not appreciate this and several abortions did occur. However, fortunately several of these women seemed to have more regular periods after the abortion and became pregnant again carrying through the second time all right.

In the cases of primary ovarian dysfunction thyroid extract is used to stimulate metabolism when it is possible to do so. These women usually have a near normal basal metabolic rate. Estrogens are given cyclically to maintain the pituitary-ovarian rhythm and to control the associated symptoms. Pelvic heat is also used at times to improve the ovarian circulation. If these measures fail, low-dosage irradiation is given over the ovaries only, as a rule. If the woman is not having hot flushes, it apparently does no harm to give irradiation over the pituitary also, though I doubt that any added benefit is gained. If the young woman is having no menses, low-dosage irradiation may be given at any time. If irregular menses are still present, the treatment is best given about the twenty-fourth day after the onset of a period. If it is effective, menstrual bleeding will ensue in four or five days and another period will occur again in twenty-eight days. It is well to wait three months to see the effect of a treatment. The treatment may then be repeated if the response has not been sufficient.

Before we had potent estrogens to give cyclically, we found that the effects of irradiation would cease after three or four months and treatment would have to be repeated. In recent years we have found that when we continued to give estrogens cyclically once we had established a cycle or a regularity for a few months the periods continued to occur regularly.

In cases of young unmarried women who do not want to become pregnant, I never urge use of irradiation, for symptoms they may be complaining of usually can be otherwise relieved.

We do not know how the effect of irradiation is produced but from work done in our laboratory with comparative low-dosage irradiation over rats' ovaries it would appear to produce a congestion only which may liberate a hormone, presumably estrin. In some way a rhythm is established because

with irradiation alone menses tend to be established and to occur regularly for three months at least. After that time the rhythm again becomes irregular.

Irradiation over the ovaries seems especially indicated in cases of amenorrhea thought to be due to retained corpus luteum or follicle cyst. Some gynecologists reserve low-dosage irradiation for use in these cases only. They use it when they cannot rupture such a cyst or express the corpus luteum manually. Slight nausea is often experienced after irradiation and a few women have temporarily lost the hair over areas where the treatment was given. These are the only side effects and no woman to my knowledge has complained about them.

There has been much criticism of low-dosage irradiation and especially of that centered over the pituitary because the pituitary makes many other hormones even more vital than the gonadotropic hormones and interference with the production and secretion of these is feared. No case in point has been reported to my knowledge.

In low-dosage irradiation for primary ovarian failure I have not noticed any added value in treating the pituitary but neither have there been any ill effects if hot flashes were not being experienced. The only questionable ill effects may have been in the cases of sterility and normal menses that I have mentioned.

In cases of amenorrhea of more than one year's duration, if only one method of treatment were available, I would prefer low-dosage irradiation. It has proved to be the best single method of therapy in such cases. Combined therapy has been somewhat more effective; that is when necessary, giving thyroid extract enough to raise the basal metabolic rate to +3 per cent and holding it there and then administering ovarian hormones, particularly the estrogenic, cyclically for three months at least before irradiation, again after treatment and on through a pregnancy, if one ensues.

OVARIAN TUMORS IN INFANTS AND CHILDREN*

MAURICE EDWARD COSTIN, JR., AND ROGER L. J. KENNEDY

More than 200 cases of ovarian tumor in infants and children have been reported in the literature. In approximately a third of these the tumors were simple multilocular cysts, in a fourth dermoid cysts, in more than a third carcinoma or sarcoma. In recent years the diagnosis of sarcoma and carcinoma of the ovary in children has become much less frequent, and it seems likely that many of the tumors which were reported as sarcoma or carcinoma in the older literature were probably granulosa-cell tumors or dysgerminomas.

Simple cysts are relatively common ovarian tumors in infants and children. In our series of twenty-two cases there were seven cases of simple cysts, an incidence of 31.8 per cent. Pain in the abdomen is the outstanding

* Abstract of paper submitted to the American Journal of Diseases of Children.

symptom, and torsion of the pedicle is a frequent complication. The latter event occurred in five of our seven cases, an incidence of 71 per cent. Simple cysts with twisted pedicles are frequently confused clinically with appendicitis or appendiceal abscess.

Cystadenoma of the ovary is rare in children. The three in our series were all in children fourteen years of age, who had reached the age of puberty. Cystadenocarcinoma of the ovary in children is correspondingly rare.

Teratomas are the most common ovarian tumor in children. In our series there were ten cases, an incidence of 45.5 per cent. The dermoid cyst variety of teratoma was more common than the embryonic type; there were seven dermoid cysts and three embryonic teratomas in our cases. The predominant symptoms are abdominal tumor and pain. Roentgenograms are useful adjuncts to the preoperative diagnosis of dermoid cyst. The dermoid cyst type of teratoma is usually benign, but the embryonic type must be considered as potentially malignant and frequently is.

One case of dysgerminoma occurred in our series, an incidence of 4.5 per cent. Dysgerminomas are unusual in that they frequently are associated with pseudohermaphroditism or genital hypoplasia. Opinions concerning the malignancy of dysgerminomas vary, but it is safest to consider them as definitely malignant tumors and treat them as such with radical surgical procedures and postoperative roentgen therapy.

Granulosa-cell tumors may occur in infants and children of any age but are uncommon. There was one case in our group, an incidence of 4.5 per cent. Granulosa-cell tumor is a rare cause of sexual precocity in children and must be considered in the differential diagnosis of this condition. The incidence of malignant granulosa-cell tumor in children is low.

SIMULTANEOUS INTRA-UTERINE AND EXTRA-UTERINE PREGNANCY*

ROBERT W. DEVOE AND JOSEPH HYDE PRATT

The most significant point we encountered in our study of simultaneous intra-uterine and extra-uterine pregnancy was the drop in the maternal fatality rate from an over-all figure of 19 per cent to one of 1.4 per cent, which is compatible with a more modern concept of surgical risk. The lower rate is, of course, due to earlier diagnosis of the ectopic condition, earlier operation and replacement of the blood and fluid loss. The replacement of blood promptly is the largest single recent factor in the reduction of fatality rates since everyone has agreed for years that the only treatment for ectopic pregnancies is early operation.

There was but one maternal death in the series since 1935, and for this reason we felt that the added complication of an intra-uterine pregnancy did not appreciably increase the surgical risk. This death occurred after a two day labor and cesarean section, at which a mummified fetus was found

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double pregnancies, when it occurs, is the presence of two corpora lutea in the ovaries, indicating the possibility of two conceptions.

The treatment of these patients is that of any patient with an ectopic pregnancy, namely, early exploration. If an intra-uterine pregnancy is also found, the patient can be given very definite hope of bearing a living child.

THE INTRA-UTERINE PACK IN THE MANAGEMENT OF POSTPARTUM HEMORRHAGE*

LOIS A. DAY, ROBERT D. MUSEY AND ROBERT W. DEVOL

Control of postpartum hemorrhage continues to be one of the highly important problems which are encountered by obstetricians. In the presence of postpartum hemorrhage which has not been controlled by oxytocic drugs or by abdominal and sometimes bimanual uterine massage, the use of the intra-uterine iodoform pack or tamponade for many years has been prominent among the active hemostatic measures we have employed.

DEATHS CAUSED BY OBSTETRIC HEMORRHAGE

There has been a striking decrease in the maternal death rate in this country in somewhat more than a decade. This trend is more or less nation-wide. The lowered maternal mortality rate has been caused by sharp reduction in two of the leading causes of maternal deaths; namely, puerperal sepsis and the toxemias. Maternal mortality caused by obstetric hemorrhage, however, has remained practically constant, except for minor fluctuations. For example, vital statistics of the State of Minnesota show that in the year 1934 the maternal deaths from puerperal sepsis, toxemia and hemorrhage were approximately twenty, eight and six, respectively, per 10,000 live births. In the year 1940, the number of deaths from sepsis, for the same number of live births, had decreased to nearly five; deaths from toxemias had decreased to a little more than four; but the number of deaths from hemorrhage had not diminished.

No doubt a wider application of the principles of adequate prenatal care, of conservative and aseptic management of labor, and the employment of chemotherapy have been important factors in the lowering of the maternal mortality rate of the toxemias and sepsis. However, these factors, in addition to more advanced obstetric education and an increase in the number of patients hospitalized for obstetric complications, also should have helped lower the incidence of obstetric hemorrhage.

It is not our purpose in this paper to review the whole subject of obstetric hemorrhage. Among the various causes of such hemorrhage, that which occurs postpartum is responsible for the largest proportion of maternal deaths from hemorrhage. Analysis of the management in such cases has shown that, although deaths from postpartum hemorrhage are not entirely preventable, under ideal conditions they are almost preventable. Among

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these ideal conditions are adequate prenatal care, conservative management of labor and its third stage, hemostasis and the replacement of loss of blood volume.

OPINION CONCERNING THE INTRA-UTERINE PACK

Review of the literature furnishes ample evidence that the employment of the intra-uterine pack for postpartum hemorrhage is a controversial subject.

Cosgrove, Leff and Hunter indicated that the use of such a pack should be kept to a minimum; they asserted that the postpartum use of uterine tamponade is unphysiologic, that it holds open the uterine sinuses, thus allowing loss of blood to continue, and that the uterus then distends rather than contracts, so that a hemorrhage which otherwise would be revealed is converted into a concealed hemorrhage. These writers said that they employ oxytocic agents and manual compression in the control of the uterine loss of blood, and that they may even maintain this compression for a prolonged period. Sherrick, Davis and others among the obstetricians who write about the management of postpartum hemorrhage do not mention the use of intra-uterine packs. The use of the hot intra-uterine douche as a hemostatic measure, before resort to packing, was advised by Corbet and DuPuy; this procedure seems to enjoy especial favor among British authors. The douche employed is carried out with either hot water or hot dilute acetic acid.

A large number of obstetricians, Pastore and Stander, Falls, DeLee and others have said that intra-uterine tamponade should be used as soon as it becomes evident that postpartum uterine hemorrhage is not being controlled by the usual available measures. These authors asserted that the intra-uterine pack acts in two ways to control the bleeding: (1) by actual tamponade, and (2) by serving as a foreign body to stimulate uterine contraction. The authors referred to were in general agreement that when packing becomes necessary, it should be done without delay.

The type of pack used varies, and many writers have said that this is of great importance. Falls, in 1937, used a pack moistened with a 1 per cent solution of cresol (lysol); DeLee in 1938 recommended use of a pack moistened with an 0.5 per cent solution of cresol (lysol); Soule used plain, iodoform or sulfanilamide gauze packs. Randall remarked that it is not important to argue about the type of pack to be used, but that it is important, after the decision to pack has been reached, to do it quickly and correctly.

THE PRESENT STUDY

Third Stage of Labor.—We wish to outline briefly the management, in general, of the third or placental expulsion stage of labor which we have followed. This procedure has varied somewhat in the course of nearly thirty years.

Before proceeding with a description of the management of the third stage of labor, we should like to mention administration of the extract of the posterior lobe of the pituitary gland as the second stage ends. We have almost never used this extract in the course of labor. The exact time of injection has varied from time to time; usually the extract has been injected directly after delivery of the baby's head or shoulders or entire body. For

two years it was the practice to inject the extract immediately after expulsion of the placenta. However, for the greater part of this period it has been customary to inject intramuscularly 1.0 c. c. of alpha-hypophamine (pitocin) during delivery of the head and shoulder of the baby.

Because of the controversial nature of this subject, we feel we should state that in our management of the third stage of labor, we have been mindful of the mechanism of placental separation and expulsion. Also, it may be stated that we have followed with reasonable uniformity the rule of withholding massage of the uterus until symptoms indicate that placental separation has occurred. When evidence of separation of the placenta is present and the placenta has not been expelled spontaneously, or if copious bleeding occurs, the placenta is delivered by simple expression. If the placenta is retained without signs of separation for more than twenty minutes, or if bleeding persists, an attempt is made to deliver the placenta by the *Credé* maneuver. Failure of this attempt calls for a rest of at least five minutes to permit relaxation and perhaps separation of the placenta, after which the *Credé* maneuver is repeated at intervals of, perhaps, ten minutes, for approximately an hour post partum. Delivery of a retained placenta by the *Credé* maneuver is facilitated, in some instances, by sufficient anesthetization of the patient to relax the uterus. In case the placenta has not been delivered within an hour, or in case bleeding requires interference before this time has elapsed, the patient is anesthetized and the placenta is delivered manually.

After delivery of the placenta, an atonic uterus or persistent bleeding indicates the need for vigorous massage of the uterine fundus and, usually, for the intramuscular or preferably intravenous administration of an additional oxytocic agent in the form of an active, aseptic ergot preparation.

Indications for Intra-uterine Packing.—If bleeding continues to be excessive in spite of the treatment we have outlined, the uterus is packed firmly with sterile gauze. Packing is most imperative when the uterus exhibits a continuing tendency to relax. Special instruments for packing have been tried and abandoned. The most effective results are obtained when packing is carried out as follows. Two fingers are inserted in the uterus, with the palm of the hand anterior. The gauze is carried along the fingers with a blunt-nose packing forceps or placental forceps or, in some instances, with the first and second fingers of the other hand. Washed iodoform gauze 2 inches (5 cm.) wide in 5 yard (4.6 m.) lengths is employed, and several lengths are tied together when more packing is necessary to fill the uterus completely. In cases of severe bleeding from an atonic uterus, the vagina also is packed tightly. When the delivery has been complicated by placenta previa, uterine and vaginal packs usually are placed as a precautionary measure, even though bleeding is not pronounced.

Uterine tamponade has been employed in certain cases of postpartum hemorrhage on the obstetric service at the Mayo Clinic since 1918. The procedure is carried out without undue delay as a hemostatic measure in cases in which postpartum bleeding is not readily controlled by oxytocic agents and uterine massage. From January 1, 1918, to December 31, 1945, there have been approximately 12,000 deliveries, and in the course of this period uterine tamponade has been done 267 times, an incidence of 2.3 per cent.

The indications for the employment of intra-uterine tamponade among these 267 patients are summarized in table 1. The uteruses of fifty-six primiparas and fifty multiparas were packed because of persistent uterine hemorrhage after the third stage of labor; in four of these primiparas and in seven of the multiparas clinical signs of shock had developed. The average amount of blood lost through hemorrhage by the primiparas was 690 c.c. The average amount of blood lost in the same way by the multiparas was 620 7 c.c. The low average amount of blood lost for which tamponade was done is perhaps explained by the prevailing policy of early institution of active hemostasis. After manual removal of retained placentas from twenty-seven primiparas and thirty-one multiparas, hemorrhage occurred for which intra-uterine packing was required. Undue relaxation or atony of the uterine musculature often is the cause of postpartum hemorrhage and placental retention. Because this relaxed condition of the uterus may persist after manual removal of the placenta, we believe that in these cases uterine tamponade is a valuable prophylactic measure in the event that

TABLE 1
INDICATIONS FOR INTRA-UTERINE PACKING AMONG 267 WOMEN

Condition	Primiparas	Multiparas	Combined
Hemorrhage persisting after delivery of placenta	36	50	106
Hemorrhage persisting after manual removal of placenta	21	25	46
Uterus remaining atonic after manual removal of placenta	27	31	58
Uterus remaining atonic after cessation of postpartum bleeding	11	46	57
Total	115	152	267

firm contraction is not induced promptly by other methods. Intra-uterine tamponade was employed for twenty-one primiparas and twenty-five multiparas after manual removal of the placenta, although no significant hemorrhage had appeared. Intra-uterine packing also was carried out, because of persistent uterine atony after cessation of bleeding, for eleven primiparas and forty-six multiparas. The employment of packing in these cases may be called "prophylactic" or "elective." In each case the postpartum hemorrhage seemed to be controlled, but the uterus remained in an atonic condition, and as a precautionary measure the pack was inserted, before the patient was returned to her bed.

One hundred seventy-five of the 267 patients (sixty-three primiparas and 112 multiparas) had relatively easy deliveries consisting of 139 spontaneous and thirty-six outlet forceps deliveries. The remaining ninety-two patients (fifty-two primiparas and forty multiparas) were delivered by more formidable procedures than outlet forceps. The various deliveries and their number are shown in table 2.

TABLE 2

TYPE OF DELIVERY AMONG 267 WOMEN REQUIRING INTRA-UTERINE PACKING

Delivery, type	Primiparas	Multiparas	Total
Spontaneous	41	98	139
Outlet forceps	22	14	36
Forceps unqualified	5	1	6
Low forceps	22	8	30
Mid forceps	3	2	5
High forceps		1	1
Breech deliveries (all types)	7	8	15
Versum and extraction	1	7	8
Unspecified	7	7	14
Destructive	2		2
Forceps rotation	2		2
Dührssen's and forceps	2		2
Multiple			
Twins	2	3	5
Triplets		1	1
Total	113	154	267

TABLE 3

ABNORMALITY OF PLACENTA AMONG WOMEN REQUIRING INTRA-UTERINE PACKING

	Primiparas	Multiparas
Partial placenta previa		6
Central placenta previa		2
Complete separation of placenta		1
Premature separation of placenta	1	
Abruptio placenta	2	2
Circumvallate placenta		1
Bilobed placenta		1
Succenturiate lobe of placenta		2
Total	3	15

Interesting obstetric abnormalities present in this group of 267 patients are listed in table 3. These abnormalities were chiefly defects of the placenta or placental site, which, when present are likely to be important factors in the causation of postpartum hemorrhage. There appears to have been a tendency for these abnormalities to occur in multiparas, for in eighteen cases of such abnormalities, fifteen patients were multiparas and only three were primiparas. Three patients had uterine fibromyomas.

Persistent Bleeding Despite Intra-uterine Packing.—Persistent postpartum bleeding ordinarily is controlled by a well-placed intra-uterine pack. Six of our patients, three primiparas and three multiparas, continued to bleed through the pack. The bleeding of three of these six patients was controlled effectively by repacking of the uterus. However, the hemorrhage of the remaining three patients could not be controlled by the use of oxytocic agents, massage or the reinsertion of an intra-uterine pack. Hence, abdominal hysterectomy was done.

The first of these three latter patients was a primigravida thirty-one years old. A uterine fibromyoma was discovered during her prenatal examination. Delivery was spontaneous, after an uneventful pregnancy and labor. Because of repeated postpartum hemorrhages not controlled by any of the usual measures or by snugly placed uterine tampons, subtotal hysterectomy was performed.

The second patient, thirty-seven years old, gravida IV, tripura, had bleeding from a marginal placenta previa. Artificial rupture of the amniotic sac controlled the hemorrhage from the placenta previa, and a normal infant was delivered. Postpartum hemorrhage, however, was uncontrolled and total abdominal hysterectomy was done.

The third patient, gravida IX, octipara, thirty-six years old, was delivered spontaneously after unusually rapid first and second stages of labor. The placenta was removed manually because of immediate profuse postpartum hemorrhage. Bleeding continued from an atonic uterus which was firmly packed; 1,000 c.c. of blood was transfused to the patient. The packing was removed after twelve hours; a state of mild shock ensued. The appearance of signs of peritoneal irritation and persistent low blood pressure led to a diagnosis of ruptured uterus, which was confirmed at the time of abdominal hysterectomy. Rupture of the uterus may have been caused by trauma associated with removal of the placenta, by the violence of the uterine contractions during the precipitate labor, or by packing of the uterus.

Febrile Morbidity Rates.—The morbidity rate among patients whose uteruses have been packed is not high. If the accepted standard for febrile morbidity of 100.4° F. (38° C.) persisting for two successive days exclusive of the first postpartum day is employed, then twenty-nine of the 267 patients are included in the morbidity group. This produces an uncorrected morbidity rate of 10.9 per cent, which is lower than the morbidity rate (13.1 per cent) among patients with anemia after postpartum hemorrhage for which the intra-uterine pack was not employed. Hunt reported a series of seventy-seven cases, involving the years 1934 to 1941, in which the intra-uterine pack was employed for postpartum hemorrhage; in the last five years of his series the incidence of febrile morbidity was 4.4 per cent among forty-six patients for whom the intra-uterine pack was employed.

Apparent causes for the febrile reaction in our series were infection of the breasts, one instance; infection of the urinary tract, ten instances; phlebitis and embolism, two instances; uterine infection, six instances; and undetermined cause, ten instances. If correction is made for those patients who had infection of the breasts or the urinary tract, phlebitis and embolism, the number of patients who had a febrile postpartum course consequent to packing of the uterus would be sixteen (including those who had febrile reactions of undetermined cause), an incidence of 6 per cent.

Fatality Rate.—There was one death. The patient was a gravida IX, octipara, thirty-nine years old, in whom rupture of the amniotic sac occurred forty-eight hours prior to the onset of labor. After several vaginal examinations carried out in the home, the patient was brought to the hospital. She was delivered of triplets after prolonged first and second stages of labor associated with poor uterine contractions. The placenta was retained; after seventy-nine minutes moderate hemorrhage developed. When efforts to deliver the placenta by the Credé maneuver failed, the placenta was removed manually and the uterus was packed. There was postpartum febrile morbidity, and hemolytic streptococci were found in the uterus. The patient died on the eighth day post partum (this death occurred prior to the advent of the chemotherapeutic agents). Incidentally, no death from hemorrhage occurred in the ten years prior to the time of this report in more than 7,000 deliveries.

SUMMARY AND CONCLUSIONS

Since 1918 we have employed the intra-uterine iodoform pack as a hemostatic agent in certain instances of persistent postpartum hemorrhage. This method of hemostasis has given excellent results when it has been carried out aseptically before the loss of blood became severe.

The chief indications for uterine tamponade are persistent postpartum hemorrhage from an atonic uterus or from the placental site shock, and manual removal of the placenta.

The morbidity rate of the series of patients for whom uterine tamponade was done was not unduly high (10.9 per cent). In comparison, the morbidity rate among patients who were anemic as a result of postpartum hemorrhage and whose uteruses were not packed was 13.1 per cent. The one death in the series presents convincing evidence of the danger of carrying out obstetric procedures through a contaminated birth canal. Perhaps, if such a patient were admitted to the obstetric service today, the use of penicillin or chemotherapy might alter the outcome.

One of us (Mussey) has employed the intra-uterine iodoform pack for more than thirty years. In that period only one patient has exhibited sensitivity to iodine. The reaction consisted of slight generalized erythema which appeared after two successive deliveries in which an intra-uterine pack of iodoform gauze had been employed. The first episode was thought to be a reaction to barbiturates, but after the rash had appeared for a second time it was attributed to sensitivity to iodine.

Available evidence indicates that the employment of the intra-uterine pack to assist in control of persistent postpartum hemorrhage has a definite place in the management of this condition.

CIRCUMVALLATE PLACENTA*

ARTHUR B. HUNT, ROBERT D. MUSSEY AND JOHN E. FABER

The subject of circumvallate placenta does not appear frequently in the obstetric literature. One of us (A. B. H.), who previously had become interested in this subject through the suggestion of Dr. W. J. Dieckmann, discussed it in 1935 and reported two cases. Since then, our interest in this subject has prompted closer inspection of placentas and has led to the collection of additional data, particularly of data relating to clinical symptoms and fetal mortality.

In approximately half of the instances of circumvallate placenta that we have observed, the symptoms somewhat resembled those of placenta previa or of premature separation of the placenta. We, therefore, feel that it is worth while at this time to compare the symptoms of these three conditions. In several instances, circumvallate placenta occurred in more than one pregnancy in the same case. Its co-occurrence with placenta previa also has been noted.

Circumvallate placenta is an anomaly which has been of interest to obstetricians chiefly from anatomic and pathologic viewpoints. Williams, Goodall and others have written complete descriptions of this anomaly, have cited the theories of other authors as to its formation and have advanced their own plausible theories for its pathogenesis. Williams quoted various German writers, notably Herff, Bayer, Seitz and others, who said that obstetric complications, such as abortion, unexplained bleeding, premature labor and anomalies of the third stage of labor, may result from circumvallate placenta. However, both Williams and Schuman have stated that in their experience the anomaly had no clinical significance. On the contrary, Hobbs and Rollins who, in 1934, reviewed their observations in seventy-nine cases of this condition in a period of thirteen years found that obstetric complications were present in thirty-nine of the cases. The fetal mortality rate in their series was 43 per cent, which is higher than that for most obstetric conditions except perhaps for abruptio placentae, severe toxemia and rare instances of rupture of the uterus.

We shall review briefly the derivation of the term "circumvallate placenta," the probable pathogenesis of the condition and the anomalous structure to which its symptoms appear to be related. It will be recalled that the entire surface of the embedded amniotic sac is covered with villi which exhibit a profuse growth usually in the area most closely approximated to the uterine wall. As the placenta develops, that portion of the chorion which overlies this profuse growth of villi is called the "chorion frondosum" while the part of the chorion from which the villi have atrophied and disappeared is called the "chorion laeve." The chorion frondosum has a smooth glistening fetal surface which is called the "placental plate." The placental plate has definite limits, the extent of which is determined by several factors which will not be considered here. The normal growth of the chorionic placental plate is determined usually by the size of the placental site, which in turn is related to the growth of the uterus and its contents.

* From the New Orleans Medical and Surgical Journal, 100:295-297 (Nov.) 1917.

The life cycle of the placenta covers a scant nine months. In the course of this time, as Goodall has aptly stated, the placental growth encompasses a lifetime—childhood, adolescence, maturity and senility. In some placentas, as in tissues of the body, degenerative changes may occur relatively early. In fact, infarction and sclerotic changes, which may appear early in gestation along the border of the placental plate, tend to interfere with the blood supply so that growth of the placental plate cannot keep pace with the increase in size of the growing placental site. In such cases, an outgrowth of villi may extend beneath and beyond the border of the chorion frondosum as an expression or attempt on the part of the placenta to maintain its function of nourishing the fetus. This outgrowth of villi causes them to pile up beyond the limits of the chorion frondosum and here they are covered only by the chorion laeve, which is thus raised up from the wall of the uterus and put under tension by the vigorously growing villi. As this piling up of villi occurs outside the more or less fibrous limit of the chorion frondosum or placental plate, it may partially or completely surround the circumference of the placental plate with a mass of villi which is elevated above the level of the plate and gives rise to the term "circumvallate." It is along this circumference that the increasing tension may cause a tear in the tissue and produce bleeding and sometimes seepage of amniotic fluid.

Forty-seven instances of circumvallate placenta were observed among 8,661 consecutive deliveries on the service of the Section on Obstetrics and Gynecology of the Mayo Clinic from January 1, 1934 to December 31, 1946, inclusive. Prior to January 1, 1934, we had not always been alert to observe and record cases in which this anomaly was present and it is quite probable that some instances may have been overlooked since that date and that many more than forty-seven instances actually occurred. However, it is probable that the condition of the placenta was noted in all cases in which symptoms were produced. This supposition is strengthened by Hobbs and Rollins who reported finding this anomaly in seventy-nine cases. In only forty-five of these cases was the pregnancy at or near term. Hobbs and Rollins also noted a ratio of one instance of circumvallate placenta in fifty pregnancies while we recorded one in 188 pregnancies.

In twenty-three of the forty-seven instances, the anomaly did not produce any clinical symptoms. These twenty-three instances of the anomaly occurred in twenty-two cases. The twenty-four instances of the anomaly which produced symptoms occurred in nineteen cases; two instances of the anomaly occurred in each of three cases and three instances occurred in one case.

In standard textbooks on obstetrics, scant mention, if any, is made of the clinical importance of circumvallate placenta. This may be due to the fact that the anomaly frequently does not produce any symptoms that are of clinical importance. As we have just stated, there were no important symptoms in twenty-three of the forty-seven instances of this anomaly observed at the clinic. In these twenty-three instances, the duration of gestation averaged thirty-nine weeks and a fetal death occurred in only one instance. In this instance, the fetus died three weeks before delivery. A history of bleeding was obtained in only two of the twenty-three instances. In each of these two instances, the bleeding occurred prior to the fourth month of gestation. On the other hand, in fifteen of the twenty-four

instances in which the anomaly produced symptoms that were considered important clinically, bleeding or spotting with blood or drainage of fluid occurred before the fourth month of gestation.

In nine instances, including some of those in which early bleeding persisted or recurred, uterine bleeding occurred in the last half of pregnancy. In seven instances the bleeding was due to circumvallate placenta, while in two instances placenta previa also was present. In these two instances, the placenta previa was undoubtedly of greater importance clinically. Placenta previa is encountered in approximately one of every 200 pregnancies. Since it occurred in two of the forty-seven instances of circumvallate placenta, one may question whether some factor affecting nidation may not be an etiologic factor in both conditions.

In five of the seven instances just mentioned, the bleeding was of such severity, grade 2 to grade 3 (on the basis of 1 to 4) that it was thought, in the prepartum period, to be caused by premature separation of the placenta.

TABLE I

ONSET OF LABOR AND FETAL SURVIVAL IN TWENTY-TWO INSTANCES OF CIRCUMVALLATE PLACENTA WITH CLINICAL SYMPTOMS*

Onset of labor, weeks of gestation	Instances	Fetal survival
20 to 24	3	0
25 to 29..	5	0
30 to 34.	5	2
35 to 38	5	5
39 to 40.	4	4
Total	22*	11 (50 per cent)†

* Two instances in which placenta previa was associated with circumvallate placenta have been excluded from this table.

† The fetal survival rate in the entire forty-seven instances of circumvallate placenta was 74 per cent.

In fifteen instances, the amniotic sac ruptured spontaneously preceding the onset of labor. In the majority of these instances, it ruptured before the thirty-fourth week of gestation; in seven instances, fluid (hydrometra) drained for from one to ten weeks prior to the onset of labor, which in each instance was premature. Examination of the placenta indicated that, in all probability, tearing occurred at the fibrous ring which marks the border of the chorion frondosum or placental plate and that this was caused by the continuing growth of placenta while the insertion of the membranes remained stationary.

Rupture of the membranes preceding the onset of labor, which occurred in fifteen or a third of the forty-seven instances, or in three fifths of the instances in which symptoms were present, is of distinct clinical importance because it usually is followed by premature labor and commonly by death of the prematurely born infant.

In the twenty-four instances in which the circumvallate placenta produced symptoms, the fetal mortality was 50 per cent. The mortality was chiefly attributable to prematurity although some extremely premature babies survived as indicated in table 1. The fetal mortality rate in the forty-seven instances was 21 per cent. There were no maternal deaths although one patient (who did not have placenta previa) required a transfusion of blood.

When uterine bleeding occurs during pregnancy, it is necessary to determine, if possible, the cause of the bleeding, and it is especially important to rule out the more serious causes of maternal hemorrhage, that is, placenta previa and abruptio placentae. This usually can be done readily by the history and by careful physical and roentgenologic examination. Roentgenologic examination has not proved to be of accurate value before the

TABLE 2

DIAGNOSTIC FEATURES OF CIRCUMVALLATE PLACENTA AND PLACENTA PREVIA

Circumvallate placenta	Placenta previa
Bleeding prior to viability is not uncommon.	Bleeding more common after period of viability
Bleeding usually slight and often accompanied by uterine contractions.	Bleeding often profuse, recurring and painless
Seepage of amniotic fluid may occur.	No seepage of amniotic fluid.
Vaginal examination does not aid in the diagnosis.	Vaginal examination may disclose positive findings.
Roentgenologic examinations, including placentograms, do not reveal any abnormality	Roentgenologic examinations, including placentograms, may disclose positive findings after the seventh month.

eighth month of gestation. Table 2 shows the distinguishing features of circumvallate placenta and placenta previa, and table 3 shows the distinguishing features of circumvallate placenta and abruptio placentae. In several instances, it was impossible to distinguish between partial pre-

TABLE 3

DIAGNOSTIC FEATURES OF CIRCUMVALLATE PLACENTA AND PREMATURE SEPARATION OF PLACENTA

Circumvallate placenta	Premature separation of placenta
Hemorrhage is evident.	Hemorrhage is commonly concealed.
Shock is not present.	Shock may be present.
Uterus relaxes between contractions.	Tonic uterine contractions.
Toxemia is unusual	Toxemia is relatively common
Bleeding prior to viability is not uncommon.	Hemorrhage more likely to occur in course of period of viability.
	Evidence of fetal distress or death.

mature separation of the placenta and circumvallate placenta until the placenta was inspected.

MANAGEMENT

Only scant comment can be made concerning the management of this condition because only a presumptive diagnosis can be made until the placenta can be inspected. In a case in which *hydorrhea gravidarum* develops, an effort should be made to prevent infection by the daily instillation into the vagina of one of the newer nonirritating, liquid antiseptics.

The management of bleeding during pregnancy, in the absence of evidence which will permit a positive diagnosis of placenta previa or of *abruptio placentae*, is one of expectancy. This requires great patience on the part of both the patient and physician. The patient must remain in bed, perhaps for many weeks, and the physician must have the forbearance to defer operative methods of delivery, such as cesarean section, unless symptoms indicate that this method of delivery is urgent.

COMMENT

One or more of the following signs or symptoms were observed in twenty-four of forty-seven instances of circumvallate placenta: (1) signs of threatened, but not inevitable, abortion; in many instances these signs recurred or did not subside, (2) prolonged but seldom profuse vaginal bleeding; (3) intermittent uterine contractions, and (4) early rupture of the membranes with *hydorrhea* followed eventually by premature labor, sometimes prior to the third trimester of pregnancy. If *hydorrhea* is present, prognosis for the fetus is poor.

The maternal hazard is due to hemorrhage and potential infection. The hemorrhage is seldom profuse and no instance of death or even shock from hemorrhage occurred in the cases reported by Hobbs and Rollins. Three patients in our series received blood transfusions; two of these also had placenta previa.

The danger of infection is potential because of the presence of blood in the lower part of the genital tract for a more or less prolonged period and because of the occasional (in ten instances of our series) prolonged period of time intervening between rupture of the membranes and labor. Postpartum fever occurred in two instances.

The fetal mortality was 24 per cent in the forty-seven instances of this anomaly. The anomaly was observed in forty-seven of 8,661 deliveries (1:188).

Repeated instances of circumvallate placenta in the same case have not been reported previously. We have observed five cases in which the anomaly occurred on more than one occasion. In four of these cases the anomaly was accompanied by symptoms of clinical importance. One of these patients had three deliveries each complicated by circumvallate placenta; all three babies survived, although two of them weighed only 1,270 and 1,360 gm. respectively. Two of the mothers, who each had this complication on two occasions, lost the infants prematurely. Almost all of the women who had a recurrence of circumvallate placenta had other pregnancies which were not complicated by this anomaly and a majority of the women who had only one pregnancy that was complicated by this anomaly had other

uncomplicated pregnancies and gave birth to living children at full term. It is evident that there is a definite tendency toward the recurrence of circumvallate placenta which occurred nine times among four of the nineteen patients who had clinical symptoms.

Circumvallate placenta is probably one of the few known etiologic factors in the condition known as *hydorrhea gravidarum*, although it does not explain all instances of this condition, especially those in which the pregnancy proceeds to term. Circumvallate placenta is an obstetric entity of definite fetal and some maternal significance which should be kept in mind when one is confronted with unaccountable bleeding in the course of pregnancy. The frequency of the occurrence of circumvallate placenta and the fetal hazard of this condition are not generally appreciated. Conservative management of protracted slight bleeding or of *hydorrhea* during pregnancy requires great patience on the part of the patient, her relatives and the physician. In a number of instances, patience has been rewarded by the survival of a prematurely born infant.

CONGENITAL ABSENCE OF THE VAGINA*

VIRGIL S. COUNSELLER

The surgical treatment of congenital absence of the vagina constitutes a most interesting chapter in gynecology. Like the treatment of other anomalies, it has gone through many changes, with successes and failures, and, ultimately, a method of correction evolves which becomes simple, easy of execution, attended by low mortality and morbidity rates, and which produces a high percentage of good results. There always will be some poor results and even failures in the management of any congenital anomaly by virtue of the defective quality of the tissues with which the surgeon must work.

THE PRESENT STUDY

At the clinic we have seen seventy-six patients with congenital absence of the vagina. For seventy patients the technic of McIndoe was employed, in which a lucite mold, covered by a Thiersch skin graft taken from the abdomen or thigh, was used. For six patients simple reconstruction was done, in which a lucite mold was left in the vaginal tract without a skin graft.

Analysis of Cases.—The age of these patients ranged from fourteen to forty-nine years. Twenty-one were less than twenty years old. Forty-eight were less than thirty years old. Six were less than forty, and one was forty-nine years of age. The last patient we treated had undergone a Baldwin operation, performed some years previously, which was a failure. The McIndoe operation was successful. Sixty-six of the patients were single and ten were married.

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Not all the patients were studied for anomalies of the urinary tract, but of those studied, sixteen were normal in this respect and nineteen had some type of anomaly. Of the nineteen, six had a pelvic kidney, five had a solitary kidney, three had duplicated ureters or pelvises, two had pyelo-ureterectasis, one had a malfunctioning kidney, one had a solitary fused kidney, and one previously had undergone nephrectomy for an unknown reason. Four had incomplete development of the uterus and bilateral hematosalpinx and endometriosis. In each instance there was complete absence of the cervix; hence, abdominal hysterectomy was performed. In one patient in this group (reported on by Ferris) the cervical canal was opened when the vaginal tract was reconstructed; this was followed by normal menstruation.

RESULTS

Of the seventy patients in whom skin grafts were used, fifty-five obtained excellent results, although for two it was necessary to do a secondary grafting procedure. In one of these the graft completely sloughed out during an attack of acute exfoliating dermatitis. For ten of the patients the result was considered to be fair, since some had granulations which would not epithelize and produced slight contracture, although seven of these who are married have said that their sexual relations are entirely normal and satisfactory. In five cases the results were considered to be poor or failures; they were due primarily to infection, with incomplete take of grafts, resulting in contracture and stenosis. Three of these patients were unco-operative, and refused to wear the mold. Of the six patients in whom no graft was used, all have obtained excellent results. The vaginas have completely epithelized; there are no contractures, and the vaginas are of normal depth and normal mobility. Nineteen patients have been married since their operation, nine were married before surgical treatment. Hence, twenty-eight of these heard from are married and all, at the time of this report, had normal marital relations. Thirty-two were still single and sixteen had not been heard from, at the time this paper was written.

COMMENT

Several points of clinical importance concerning patients with congenital absence of the vagina should be stressed. If they do not have abdominal symptoms of menstruation or palpable, painful adnexal masses, there is no need for surgical interference unless marriage is contemplated. The operation will not improve the general health, but if the patient is operated on, she may have a happier outlook on life, knowing that she can be married without subsequent difficulties if the opportunity presents itself. The psychologic attitude and frigid character of a few such patients is such that any idea of their marriage should be discouraged, because the probability of incompatibility and extreme unhappiness is very great.

If the patient has a functioning uterus and it is possible to construct a vagina and establish menstruation, as did McIndoe and Bannister in their case and Ferris in his case and a few others that have been reported, such an outcome represents the ultimate in success. However, the number of patients in whom this can be done will remain very small, because the vast majority of such patients either have no uterus at all or one that has very little functioning endometrium and will require removal to obtain relief of

pain. Hematosalpinx and endometriosis probably are associated in such cases. Miller, in a personal communication, said he had never seen an instance of endometriosis in congenital absence of the uterus and vagina—a very pertinent observation in respect to the etiology of endometriosis.

Congenital anomalies of the urinary tract in association with congenital absence of the vagina are of very frequent occurrence, so that the upper part of the urinary tract should be investigated prior to any surgical operation to correct the absence of the vagina. When one kidney is ectopic, it usually is in front, or to one side, of the sacrum. In this position it will interfere with the obtaining of proper depth of the vagina, and is very likely to be traumatized during sexual relations. Moreover, this ectopic kidney also may be solitary. A fused kidney also may lie in the pelvis. A hydronephrotic kidney in the pelvis has been diagnosed as an ovarian cyst. Removal of such a kidney is not a simple procedure, since it has a fixed position because of the entrance of many anomalous blood vessels at both the upper and lower poles, as well as at the hilus. Anomalous insertion of a ureter or a duplicated ureter into the bladder may result in formation of a ureterovaginal fistula.

The ability of the vaginal tract completely to epithelize itself without skin graft is of tremendous importance. In enough cases, treatment has been based on this method, with success, to enable us to say that in certain instances a graft is not necessary. The difficulty is to select the patients for whom the grafting procedures should be used. We believe that in those cases in which the vaginal tract can be opened up easily and satisfactorily, without bleeding from the venous plexus on each side near where the uterine vessels ordinarily would enter, and when there is no difficulty in elevating the peritoneum, the grafting procedure probably does not need to be used in the vaginal tract. Where this epithelium comes from, in such an instance, is a debated question, but it probably arises from the lower segment of the vagina and also from some buds of epithelium from remnants of the müllerian ducts. During dissection one of these buds was picked up from beneath the bladder. It was immediately subjected to biopsy, and was found to be squamous epithelium. This epithelization might be accelerated by administration of estrogenic substances. Ayre took smears from an artificial vagina, in which no graft had been used, and showed the new lining to be reacting in a cyclic manner to ovarian hormones in the same manner as a normal vagina does.

If there is a complete take of a Thiersch graft, it produces an excellent result, provided the mold is worn long enough. Our only difficulty with the Thiersch graft has been that, occasionally, there will be one or more areas in the vagina which are devoid of skin, and it is unlikely that any epithelium will extend from the remaining skin graft to cover the defect. It is usually necessary to regraft these areas. It is of interest, also, to note that granulation rarely occurs in a vagina in which the grafting procedure has not been employed. If, however, granulation does take place in such an instance, the granulations are smaller and are situated in the areas of the bleeding points which occurred during the original dissection.

We believe, therefore, that it is possible to determine at the time the vaginal tract is opened whether or not a skin graft of the Thiersch type will be indicated. If the dissection has been difficult, as frequently is true

in a secondary operation, bleeding should be accurately controlled and the tract grafted over a nonirritating mold. If the tract can be easily opened, if there is no bleeding of consequence, and if some granular buds of epithelium can be demonstrated, and proved by biopsy, at the reflection of the peritoneum from the base of the bladder, we believe that such a tract will completely epithelize itself without the need for a graft.

One point to be observed in the subsequent treatment of these patients applies to both methods (that is, use or nonuse of a graft), and that is the "contraction factor." If the factor of contraction in these new vaginal tracts is disregarded, there will be a greater incidence of poor results and failures than if this factor is observed. McIndoe, who is primarily a plastic surgeon, is responsible for pointing this out to us. It is the one point which made the method described by Kirschner and Wagner a successful operation. Hence, I usually refer to this method as the "McIndoe procedure."

McIndoe said that the contraction factor of any canal lined by a Thiersch graft may last three to six months or longer, and that if the mold is removed before this "contraction" disappears, stricture of the new canal will ensue. Most failures or poor results are due to removal of the mold too soon. I have the greatest difficulty in convincing patients and some physicians that the mold must remain in position for at least six months or longer, and that it must be removed only for cleansing purposes or for inspection of the graft. I have had some patients who have worn the mold for two years, during the process of regrafting. In fact, I see no reason why a lightweight mold constructed of a nonirritating substance could not be worn during the entire period of the patient's sexual life, if necessary, to maintain patency. There are other parts of the body where artificial molds and braces are worn as long as the patients concerned live.

Perivaginal inflammation also contributes to contraction and shortening if the mold is taken out. It may take two to four months before all of the perivaginal and perirectal cellulitis completely subsides. This element of time is very variable, it may be more in respect to some patients than to others. The scarring and contraction of a Thiersch graft also vary among different patients.

If the vagina has not been constructed by means of the grafting procedure, a vaginal mold also is required to be worn until the entire tract has been proved by observation and biopsy to be completely epithelized. This will require a minimum of four months and perhaps longer.

SUMMARY AND CONCLUSIONS

It would seem that a sufficient number of operations for congenital absence of the vagina utilizing the McIndoe principle, with or without a Thiersch graft, have been performed in this country and abroad to permit recommendation of the procedure as probably being the best and simplest procedure for correction of this anomaly. There are, it is true, other methods which will give satisfactory results. This particular method produces a vagina which will be normal in depth, diameter and mobility. The risk of the operation is practically nonexistent. In this series there was no death. The morbidity rate will vary according to the amount of pelvic cellulitis which may occur. The operation technically is very simple, and consists only in the careful opening of the vaginal space and the use of a skin-

covered mold or use of such a mold without the skin, as the case may be. The principle of mechanical prevention of contraction of the new vaginal tract by means of a mold is the basis for success in every one of these operations. The majority of procedures in which portions of intestine or pedicle flaps are utilized are multiple-stage operations, excepting that described by Falls, which appears to be a simple and excellent procedure. I rather doubt that the functional effect which is obtained by the McIndoe operation can be attained by any other procedure.

In conclusion, it should be said that most histologic evidence indicates that the normal vagina is formed from the müllerian ducts and the urogenital sinus. If there is no evidence of müllerian ducts or epithelial buds from them, the new vaginal tract had best be constructed by means of a skin graft, particularly if there has been much difficulty in dissection. In other cases, a graft need not be used.

Seventy-six cases are concerned herein. In each case, reconstruction of the vagina was based on the McIndoe principle. In seventy cases the procedure included use of a Thiersch skin graft; in six cases operation was performed without use of a skin graft. The decision as to whether the new vaginal tract should be constructed by the use of a graft must be determined at the time of operation.

HYPERTHYROIDISM AND PREGNANCY*

ROBERT D. MUSSEY, SAMUEL F. HAINES AND EMMERSON WARD

Hyperthyroidism is an uncommon complication of pregnancy. Its reported incidence ranges from 0.03 to 3.7 per cent of all pregnancies, with an average of about 0.2 per cent. Nevertheless, dangers to the mother and fetus make it important that proper treatment be instituted promptly. Uncontrolled hyperthyroidism not only leads to a high incidence of abortions but also subjects the mother to all the hazards inherent in thyrotoxicosis. On the other hand suitable management of hyperthyroidism in pregnancy results in a fetal mortality rate not greatly higher than that of otherwise uncomplicated pregnancy and also affords control of maternal thyrotoxicosis comparable to that in nonpregnant women. Pregnancy does not seem to alter the course of hyperthyroidism in most cases.

DATA ON THIRTY INSTANCES OF HYPERTHYROIDISM AND PREGNANCY

Mussey, in 1939, reported the results of treatment in sixty-six cases of pregnancy with hyperthyroidism observed at the Mayo Clinic from 1923 to 1937, inclusive. In this paper we wish to present data on a similar group of cases from the same clinic from 1938 to 1946, inclusive, a nine-year period in which thirty pregnancies of twenty-nine patients were complicated by hyperthyroidism, for one patient had a recurrent exophthalmic goiter during a second pregnancy. In general treatment followed the plan

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outlined by one of us (R. D. M.) which we mentioned in the complete paper. An attempt was made to control mild exophthalmic goiter by oral administration of iodine in the form of Lugol's solution; if necessary, thyroidectomy was performed after preoperative preparation with iodine. Adenomatous goiter with hyperthyroidism was treated by thyroidectomy in all cases.

Of the twenty-nine patients, nine had adenomatous goiter with hyperthyroidism; eight of these nine patients underwent thyroidectomy during pregnancy and one after a spontaneous abortion. Twenty of the twenty-nine patients had exophthalmic goiter during one pregnancy and one of these had a recurrence of the exophthalmic goiter with a subsequent pregnancy. In seventeen of the twenty-one instances of exophthalmic goiter thyroidectomy was performed during pregnancy. In sixteen it followed treatment with iodine and in one thionracil and later iodine were used. In three of the twenty-one instances the thyrotoxicosis was controlled adequately with iodine during pregnancy, and in one thyroidectomy was performed after spontaneous abortion which began before definite treatment of the thyrotoxicosis had been started. In five instances the exophthalmic goiter was recurrent; treatment in four of these consisted of thyroidectomy during pregnancy and the symptoms in the fifth were controlled by iodine. There were no maternal deaths. In all instances the hyperthyroidism was well controlled when the patient left the clinic.

In ten instances the condition of the mother and fetus at termination of pregnancy is not known. The results of the pregnancy are known in twenty instances. Sixteen normal infants were born. In two instances, one of exophthalmic goiter and one of adenomatous goiter with hyperthyroidism, spontaneous abortions occurred or started before treatment of the thyrotoxicosis was initiated. In one instance of exophthalmic goiter an abortion occurred eight days after thyroidectomy. In another instance a premature infant born during the eighth month of pregnancy died a few hours after birth, this infant's mother had had a hyperfunctioning adenomatous goiter removed during the third month of pregnancy and had remained in very satisfactory condition during the rest of her pregnancy. None of the nine infants delivered at the clinic had any thyroid abnormality. The hyperthyroidism of the mothers was known to be controlled at time of delivery in the sixteen instances of full term pregnancies, one instance of premature delivery, and in one instance of the women who had abortions.

In twenty-one instances the onset of hyperthyroidism antedated the onset of pregnancy; in five the onset of pregnancy preceded the hyperthyroidism and in four the onset of hyperthyroidism was too insidious to be certain of its relation to pregnancy.

In those twenty-one instances in which the onset of hyperthyroidism preceded pregnancy, the course of the hyperthyroidism apparently was not affected appreciably by the pregnancy in nineteen, whereas in two cases the symptoms of hyperthyroidism were slightly increased during pregnancy. In none was there significant diminution of symptoms during pregnancy, nor any change in the course of hyperthyroidism that could be attributed to the pregnancy.

Ill-effects possibly attributable to thyroidectomy during pregnancy were seen in only two instances. In one case abortion in the third month of

pregnancy occurred eight days after thyroidectomy for exophthalmic goiter. In a second case a planned subtotal thyroidectomy was interrupted after removal of only one lobe and the isthmus because of the onset of uterine contractions during the operation; later in the pregnancy the other lobe was resected without incident. The patient went to term and gave birth to a normal infant.

In summary, in thirty instances in which the patients received treatment at the Mayo Clinic hyperthyroidism complicated pregnancy. Recommended treatment of the hyperthyroidism included oral administration of Lugol's solution and thyroidectomy for hyperfunctioning adenomatous goiters, and Lugol's solution plus thyroidectomy, if needed, for exophthalmic goiter. Pregnancy did not seem to influence the course of hyperthyroidism in most cases. Likewise, proper treatment of the hyperthyroidism allowed the pregnancy to proceed normally.

It is our opinion that the standard treatment of hyperthyroidism by iodine and thyroidectomy can be carried out safely in the great majority of cases of hyperthyroidism complicating pregnancy. Subsequent experience will afford more information about the relative advantages or disadvantages of treatment with antithyroid drugs in these cases. We have not had experience with the use of radioiodine in pregnant women. At the moment it would seem desirable to learn more of the possible effects of radioiodine before using it for treatment of hyperthyroidism in pregnant women.

THYROID THERAPY*

LAWRENCE M. RANDALL

The exact correlation between the function of the thyroid gland and the functions of the anterior lobe of the pituitary body and the gonads is not thoroughly explained by any satisfactorily controlled experimental or clinical work on the human being. Likewise, the results of clinical experience in this field are not based on an exact foundation. The clinical signs ascribed to hypothyroidism—except those of true myxedema, and this condition not infrequently escapes detection—are not always easily demonstrated. Estimations of the basal metabolic rate must be performed and rechecked with great care, because they are subject to error. Consequently, a diagnosis of hypothyroidism or lowered rate of metabolism without myxedema may not always be made easily.

These statements are made to emphasize the fact that the employment of thyroid extract in the treatment of disorders of function of the generative system of the human female still follows somewhat of a rule of thumb. I say this not to discredit this form of treatment, but to point out the inexactitudes of our present knowledge and to emphasize the need of careful diagnosis and control of treatment when this form of therapy is to be employed.

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Reports have been current for some time that the adequate use of thyroid extract, where indicated, has produced the best results of any hormone therapy used in gynecology and obstetrics. With this I fully agree. This seems particularly true among the younger patients. It is my impression that there is a lowered incidence of favorable results of such therapy in the latter part of the age range of menstruation. However, those of you with considerable experience can recall instances in which this form of treatment has failed even though it has succeeded in other seemingly identical cases.

Many women whose menstrual and reproductive functions have proved to be normal have had rates of basal metabolism lower than normal, with or without the clinical signs of hypothyroidism. Other patients frequently are seen with marked aberrations of these functions associated with a rate of basal metabolism well within the limits of normal. In addition, elevation of the lowered rate of basal metabolism is not always accompanied by relief of symptoms. Indeed, hyperthyroid states have been associated with the same menstrual disturbances found in the hypothyroid state.

The extremes of malfunction of the thyroid gland—hyperthyroidism and myxedema—frequently are not a problem for the gynecologist and obstetrician. We are concerned in this discussion with a group of patients designated as "hypothyroid" or preferably as those who have "a lowered rate of metabolism without myxedema." True myxedema usually is accompanied by a rate of metabolism below -30 . However, the rate of metabolism is not the deciding factor in the diagnosis of myxedema. Changes in the skin, delayed reflex recovery, alterations in the voice and cerebration, and alterations in the amount of cholesterol in the blood are part of the characteristic picture. The lower limit for a normal basal metabolic rate is said to be -10 . Between these two figures of -10 and -30 will be found the rates of the majority of those patients with lowered basal metabolic rates, associated with gynecologic and obstetric conditions. The significance of this rate probably depends on the presence or absence of associated symptoms of disturbed genital function. In addition, one should consider the presence or absence of those general symptoms and signs said to be associated with a lowered rate of basal metabolism without myxedema, increased physical and mental fatigability, intolerance to cold, and dry skin and hair.

Having established some background or philosophy concerning a lowered rate of metabolism without myxedema related to our field of medical practice, we may consider the questions of diagnosis and treatment.

The history should include a note regarding the above-mentioned general signs and symptoms of a hypothyroid state. However, the presence or absence of them should not deter us from estimating the basal metabolic rate. This examination should be made in all cases of disturbances of menstrual and reproductive function. Naturally, when organic pelvic disease is present, an added factor must be taken into consideration. Regardless of the results of the initial test, another estimation should be obtained. Technical errors are not uncommon; frequently the patient is not a good test object at the initial experience. We should be certain that the true rate of basal metabolism has been obtained. In our experience, estimations of the amount of cholesterol in the blood have not been of value in patients who have an uncomplicated lowered rate of metabolism without myxedema.

When the rate of basal metabolism has been satisfactorily determined

and treatment with desiccated thyroid extract is to be instituted, we should remember that the effective therapeutic dose and the tolerance are problems peculiar to the given patient. It is necessary, by means of trial, time and repeated estimations of the basal metabolic rate, to determine the safe and effective dose—too much may do harm and too little will be ineffective. Once the daily dose of desiccated thyroid extract that will maintain the basal metabolic rate in the vicinity of 0 has been determined, that dose should be continued until a thorough trial has been secured. In my opinion, the minimum for this is one year, during which period estimations of the basal metabolic rate are made from time to time.

Where a significantly lowered rate of metabolism has been found, elevation of the basal metabolic rate usually should be the first step in treatment. After a period during which the rate has been satisfactorily maintained without improvement of symptoms, other forms of hormone treatment may be employed as adjuncts to the treatment with thyroid extract. It seems logical to believe that without the increase in bodily efficiency produced by elevation of the basal metabolic rate, other forms of treatment have less chance of success. If therapy with thyroid extract alone or in combination is successful, the basic dose of thyroid extract necessary to maintain the elevation of the basal metabolic rate should be continued after the symptoms disappear and normal function is resumed. The duration of treatment with thyroid extract thereafter, as well as the doses employed, is a matter for individualization. Perhaps in some patients the lowered rate of metabolism is temporary, while in others it is a fundamental familial characteristic which persists.

The patient should be cautioned to continue the use of the same preparation of desiccated thyroid that was used in the elevation and maintenance of the basal metabolic rate. All thyroid preparations made by reputable pharmaceutical houses are reliable, but there is a difference in potency per unit which, if not recognized, may affect the level of the basal metabolic rate and thus the efficacy of treatment.

We prefer to elevate the rate rapidly by giving 2 to 3 grains (0.13 to 0.2 gm.) of a thyroid extract 50 per cent stronger than U.S.P. a day for three days, then giving 1 to 2 grains (0.065 to 0.13 gm.) a day for four days, after which the basal metabolic rate is again estimated. The dose is then maintained or reduced, depending on the result of the test. Another basal metabolic rate is estimated in a week. Usually, in three weeks the necessary maintenance dose is established.

When the basal metabolic rate is elevated in cases of infertility, it is particularly important to maintain the elevation if pregnancy occurs. There is an increase in the rate of metabolism as pregnancy progresses, but this has been shown probably to represent the combined metabolism of the mother and fetus, and it occurs later in pregnancy. I have observed the necessity for increase in the dose of thyroid extract in early pregnancy, and believe that the basal metabolic rate should be closely followed in these cases during the first half of pregnancy.

I have laid much stress on the estimations of the basal metabolic rate for diagnosis and control of treatment. I would re-emphasize this for the great majority of cases. However, treatment with desiccated thyroid extract is a form of stimulation, and so may compare with treatment by

means of low-voltage roentgen rays and possibly the use of extrinsic gonadotrophins. Accordingly, there are some individuals with disturbances of function of the genital tract who have metabolic rates within normal limits in whom further elevation of the rate may be used as stimulation under very carefully controlled conditions.

One must consider contraindications to elevation of the basal metabolic rate in these patients, such as cardiac disease, hypertension, renal disease and the presence of disease of the thyroid gland. There is danger in the treatment of true myxedema; hence, consultation with an internist should be secured before treatment is undertaken.

PREGNANCY ASSOCIATED WITH DIABETES*

LAWRENCE M. RANDALL

From January 1, 1933, to December 31, 1946, inclusive, 9,273 obstetric deliveries were made at the Mayo Clinic. The annual number of deliveries ranged from 384 in 1933 to 1,218 in 1946. In this period of fourteen years, we observed forty pregnant women who had diabetes. The forty diabetic women gave birth to fifty infants. No instance of multiple pregnancy was observed in these cases. Cesarean section was performed twenty-six times on twenty-two of the women. One of the infants delivered in this manner died in the neonatal period. Vaginal delivery was performed twenty-four times on nineteen of the women.† Of the twenty-four infants who were delivered through the vagina, fifteen survived, six were stillborn and three died in the neonatal period. The fetal survival rate was 96.2 per cent in the instances in which cesarean section was performed and 62.5 per cent in the instances in which the delivery was made through the vagina. All of the mothers survived.

In seven of the twenty-two cases in which cesarean section was performed, the patients previously had given birth to a dead fetus. In one of the seven cases, a stillbirth had occurred on two occasions. In four of the twenty-two cases, there was a history of neonatal death. One patient previously had been infertile, and dystocia previously had necessitated a difficult forceps delivery in one case. In three of the twenty-two cases in this group, the diabetes was difficult to control and accident to the child was feared. Toxemia was present in eight cases. In one of the eight cases, toxemia occurred in two pregnancies in which the patient was observed at the clinic. Although the toxemia responded to treatment in some cases, it still was considered an added risk to the fetus. In five of the twenty-two cases in which cesarean section was performed, diabetes was the only complication. In several cases there was more than one indication for cesarean section.

* Abstract of paper published in full in the *American Journal of Obstetrics and Gynecology*, 54:418-423 (1947).

† One of the forty patients was observed in four pregnancies. Cesarean section was performed once and vaginal delivery was completed on three occasions.

We were able to select the method of delivery in thirty-one, or 62 per cent, of the fifty instances, that is, in all of the twenty-six instances in which cesarean section was performed and in five of the twenty-four instances in which vaginal delivery was employed. In two of the five instances in which vaginal delivery was selected, spontaneous labor occurred at or near term; in three instances, labor was induced. In six of the remaining nineteen instances in which vaginal delivery was employed, the fetus was dead. In thirteen instances, labor commenced prematurely and spontaneously while the fetus was alive.

The loss of nine of the twenty-four infants delivered through the vagina merits brief comment. In four instances the mother co-operated poorly in the care of the diabetes and severe acidosis no doubt contributed to the fetal mortality. The patient who had eclampsia came to the clinic for emergency treatment after the fetus had died in utero. In the case in which premature separation of the placenta occurred, the diabetes was controlled satisfactorily and there was no evidence of toxemia. In one case, acidosis was present and no fetal heart sounds could be heard when the patient was admitted to the hospital. In two cases in which the diabetes was controlled satisfactorily and other complications were not present, the fetuses died in utero at the thirty-sixth and thirty-seventh weeks of pregnancy, respectively.

In 1936, Ryncarson and I reported seven consecutive cases in which diabetic women were delivered of infants. Cesarean section was performed in six of the seven cases; in the remaining case, the infant was delivered through the vagina. Cesarean section was the treatment of choice at the time these patients were observed. We emphasized that hypoglycemia of the newborn infant was a frequent cause of neonatal morbidity and mortality, and we recommended that cesarean section at about the thirty-sixth week of gestation should be seriously considered for the delivery of the overmature and overweight fetus of a diabetic woman. We advised watching for the development of hypoglycemia in the infant and stressed the importance of correcting this condition.

In the past ten years a considerable number of cases of diabetes and co-existing pregnancy have been reported. Until recently, the infant mortality and morbidity have not always been satisfactory although the maternal risk has been minimal in cases in which adequate co-operation has existed between the patients and their physicians. A satisfactory explanation has not been found for the previously high incidence of infant mortality and morbidity. Perhaps the excellent work of Smith, Smith and Hurwitz and of White will not serve to avoid all of the accidents to infants of diabetic mothers, for disturbances of metabolism incident to a combination of diabetes and pregnancy are necessarily complex; however, the results of correction of the imbalance between amounts of chorionic prolan and placental steroids resulted in a fetal salvage of 90 per cent and White further reported a fetal survival rate of 96 per cent in cases in which diabetic mothers had a normal hormonal balance.

My experience with this concept of correction of hormonal imbalance is limited to eight cases. In six of these cases, the infants survived. Cesarean section was performed in two of these cases and both of the infants lived. Toxemia was present in both of the cases and the diabetes was severe

("brittle") in one of the cases. In two cases, labor was induced at the thirty-fifth and thirty-eighth weeks of pregnancy, respectively, and live infants were delivered.

In four cases, labor commenced prematurely and delivery was made through the vagina. Premature separation of the placenta occurred in one of these cases. In this case, the child was stillborn. In one case, in which labor occurred at the thirtieth week of pregnancy, after coma and acidosis in the mother, the infant died in the neonatal period. In the two remaining cases, the infants lived. In one of these cases, the infant weighed 4,080 gm. when born at the thirty-sixth week of gestation. In the other case, the infant weighed 4,210 gm. and was delivered by a difficult forceps procedure.

It is to be hoped that recognition and correction of the hormonal imbalance, when present in diabetic women who are pregnant, will result in a higher percentage of normal deliveries. As is true in all obstetric conditions, a careful study of all factors involved in a given case should lead to proper selection of treatment. There is and will continue to be a difference of opinion in regard to the delivery of diabetic women.

THE SURGICAL ASPECTS OF ENDOMETRIOSIS*

VIRGIL S. COUNSELLER

I believe that there is no pelvic operative procedure that at some time is not required for endometriosis or made more difficult by its presence. Few conditions demand more surgical skill and judgment to secure the best way out of an unfortunate situation for the patient.

Since the symptoms of endometriosis per se are due to the presence of functioning ectopic endometrium, castration could reasonably be expected to cure the patients. This is no doubt true of the majority of cases, the exception to this being those cases in which the chief symptoms are due to a mass in the pelvis, obstructed loops of bowel or massive adhesions.

If one belongs to the group of surgeons who feel that the ovary serves no useful function after the age of forty years—my colleagues and I do not—then the treatment of 58 per cent of patients suffering from endometriosis resolves itself into producing either surgical or radiation castration.

My colleagues and I feel that the ovaries of patients of any age group should not be removed unless it is necessary but especially not those of patients less than forty years of age. In spite of strong convictions in this regard, it was deemed necessary to produce castration in 36 per cent of the cases in which patients were less than forty years of age because the extensiveness of the endometriosis precluded its complete removal.

If the patients who have minimal or incidental findings of endometriosis were not considered, then it would be found that of the patients who had moderate or severe symptoms and physical findings of endometriosis more than 50 per cent would require castration to relieve their symptoms. Some

* Abridgment of paper published in full in *The Journal of the International College of Surgeons* 11:29-33 (Jan-Feb.) 1943.

patients do have the endometriosis confined to one removable adnexum or this plus a few removable implants. There is no middle ground, however, either the endometriosis or the ovaries must be completely removed in order to have reason to expect a surgical cure.

This consideration is of great importance to both the surgeon and the patient. The young woman who has moderate pelvic discomfort for even six or seven days per month, once she is assured that no serious consequences will result from deferring operation, may prefer to endure this disability rather than run a 50 per cent chance of surgical castration being necessary for a cure. The woman of thirty-six or thirty-eight years of age may expect an early menopause and she may be willing to bear her discomfort with the prospects of its early termination. A high percentage of the secondary and tertiary pelvic laparotomies are required because an incomplete operation was done previously for endometriosis.

If the extensiveness of the endometriosis is such as to require castration, the castration is not usually followed by the same intensity of menopausal symptoms as is common in castration for other reasons. Many of these patients will have few, if any, symptoms. This phenomenon is explained in part by the fact that the gradual destruction of ovarian tissue by the endometriosis has progressed, at the time of operation, to such an extent that the patient has been bordering on menopause for some time. During this period she may have unknowingly made a gradual nervous adjustment which the final complete withdrawal of ovarian secretion does not upset.

There is an occasional patient less than thirty years of age for whom it seems advisable to do a palliative operation with the hope of carrying her along to an age at which castration would be less of a tragedy. A few of these patients are completely relieved and for others an early menopause makes further surgical treatment unnecessary.

In a selected group of twenty cases in which the chief symptoms of dysmenorrhea and dyspareunia were due to deep implants in Douglas' cul-de-sac which could not be removed, presacral neurectomy was done. This was combined with excision of the accessible implants and usually suspension of an adherent retroverted uterus. Owing to careful selection of patients the results of this procedure have been very good.

The difficulties inherent in doing the common pelvic operative procedures in the presence of endometriosis have received very slight attention in the literature. At times the utmost skill is required by the surgeon either to keep out of difficulty or to extricate himself from a bad situation in which he may inadvertently find himself when operating in the presence of extensive endometriosis. In the presence of this lesion mishaps are especially likely to occur.

A few examples of the difficult situations encountered are worthy of special mention. In cases of old pelvic inflammatory disease one can easily elevate an adherent retroverted fundus by working the finger down between it and the rectum. However, in cases of endometriosis one cannot do this without danger of penetrating the wall of the rectum, or of part of the muscularis of the rectum adhering to the fundus. Similarly, in separating loops of small bowel from each other or from the uterus or adnexa, special care must be taken to avoid stripping off part of their musculature before one realizes that one does not have a true cleavage plane.

Often, once the uterus has been removed, there is very little peritoneal covering left for Douglas' cul-de-sac and the lateral pelvic walls. This situation can be remedied by laying the sigmoid in the pelvis and placing a few sutures to hold it there. The pelvis is the normal location of the sigmoid, it suffers from no functional inconvenience from being sutured there and in this location it keeps loops of small bowel from becoming adherent in the pelvis.

Douglas' cul-de-sac may be entirely closed off by the rectum being drawn forward and being densely adherent to the posterior fornix and lowermost part of the supravaginal portion of the cervix. This relationship is usually best left undisturbed. Other things being commensurate, the patient's interests are better served by subtotal hysterectomy than by total hysterectomy when the latter would entail considerably more trauma and risk than the former. In such a case more than the usual care must be exercised that in closing the cervical stump a suture is not passed through the adjacent portion of the rectum.

The vesico-uterine space is often obliterated by implants which cause the bladder to be adherent to the supravaginal portion of the cervix. In separating the bladder, sharp dissection must be used. No line of cleavage is present and it is at times difficult to avoid dissecting away part of the vesical wall or opening the bladder. In closing the vagina or the cervical stump caution must be exercised lest the suture be passed through the vesical wall. It is easy to pass the suture through the vesical wall, since the field is obscured by a bloody ooze and the bladder is usually still attached to the anterior fornix instead of being displaced forward. The most common cause of vesicovaginal fistula is an unrecognized suture in the vesical wall which was placed at the time of closure of the cervical stump after subtotal hysterectomy.

To avoid injury or ligation of the ureters is probably the chief concern of every pelvic surgeon. Endometriosis shares with cervical fibroids first place as the contributing cause of such accidents. In endometriosis three factors contribute considerably to making the ureter more than usually vulnerable to injury.

First, improper orientation causes injury to a ureter in many cases. Dense adhesions prevent proper mobilization of the uterus. The field is obscured by spilled tarry material, oozing of blood from innumerable denuded areas and sponging by the assistant. Under these circumstances especial care must be taken to visualize each ureter and to avoid including it with the corresponding uterine artery when a forceps is applied to the latter.

Secondly, involvement of the paracervical tissues by endometriosis results in formation of scar tissue. Contraction of this scar tissue draws the ureter even closer to the cervix, thereby appreciably reducing the normal narrow 2 cm. space between the cervix and ureter where the uterine artery must be clamped.

Thirdly, in the ordinary hysterectomy when the cardinal ligaments are put on tension, just before the forceps are placed on the uterine artery, the ureter drops away from the cervix and the uterine artery. Endometriosis causes fixation of the paracervical tissues and lateral pelvic wall so that when traction is made on the uterus the attached ureter, instead of dropping away, is further drawn upward into the operative field.

Proper orientation is essential and the course of each ureter should be known even if it is necessary to dissect it out in its entire pelvic course. If this is done and the fact that in these cases the ureters are more than usually vulnerable is kept constantly in mind, the ureters will seldom be injured.

The chief weapon in preventing errors is the realization that with the setup at hand certain errors are more than usually likely to be committed. With this knowledge such errors can be more certainly avoided.

CHOREA GRAVIDARUM: REVIEW OF THE RECENT LITERATURE AND REPORT OF FIVE CASES*

THOMAS W. McELIN, SIM B. LOVELADY AND HENRY W. WOLTMAN

A summary of the findings in five cases of chorea gravidarum is given in the tabulation. It is impossible to draw any significant conclusions from this small series of cases. The average age of our patients was 21.4 years. Four were married and one was unmarried. Two were primigravidas and three were multigravidas. In all of these cases chorea began in the first half of pregnancy and lasted for periods varying from two and a half weeks to five months. All of the pregnancies were terminated spontaneously at term and six normal babies were born (one twin pregnancy).

Only one patient (case 1), whose condition might be described as moderately severe, required hospitalization while under our care. One other patient had been hospitalized elsewhere in the pregnancy under consideration. The therapy offered to our hospitalized patient was by no means specific and was directed essentially toward the relief of the independent or possibly associated nausea and vomiting. Both complications were relieved at about the same time. Two recent publications in the South American literature referred to the use of pyridoxine (vitamin B₆) as a therapeutic agent in cases of chorea gravidarum with gratifying results. We used this agent in the treatment of the hyperemesis in this case but also used other measures so any evaluation of the therapeutic effect of pyridoxine in this condition is impossible.

No evidence to support a toxemic etiology of this condition was present in this series, other than perhaps the nausea and vomiting mentioned in two cases. A rheumatic background was present in all of the cases. A past history of chorea was given in three cases and of rheumatic fever in two cases. Heart disease was present in three cases. In case 3, a patient who did not give a history of chorea or rheumatic fever and who had no evidence of heart disease had had scarlet fever and several episodes of tonsillitis as a child which might be classified as a rheumatic-equivalent type of background. In the terminology of Weigner, psychogenic "color" was noted in four of the five pregnancies.

* Abstract of paper published in full in the *American Journal of Obstetrics and Gynecology*, 55: 992-1008 (June) 1948.

TABULATION
SUMMARY OF FINDINGS IN FIVE CASES OF CHOREA GRAVIDARUM

Case	Age	Marital status	Choreic attacks		History of chorea		History of rheumatic fever or scarlet fever	Heart disease	Evidence of infection	Toxicogenic color*	Chorea				Termination of pregnancy	Result	Subsequent pregnancy
			Attackable	Unattackable	Unimpaired with previous pregnancy	Unimpaired with previous pregnancy					Month of pregnancy at onset	Months of continuation	Duration	Treatment			
1	30	Married	4	0	1	1	Scarlet fever	Present	None	Not present	Approx. fourth	Approx. fifth	Approx. 2 1/2 weeks	Isolates Vitamin therapy Sulfaglycine	Spontaneous	Infant living	None
2	45	Married	5	4	1	1	Scarlet fever, rheumatic fever	Probable present	Rh. factor, Absence of agglutination and positive	Present	First half of pregnancy	Approx. fifth	Approx. 6 weeks	None*	Spontaneous	Infant living	Not known
3	42	Married	1	3	0	0	Scarlet fever	Not present	None	Present	Third	1 month (?)	At least 4 months	None*	Spontaneous	Infant living (seen preg.)	One normal pregnancy without chorea
4	41	Married	1	0	0	0	Illness fever	Not present	None	Present	First	Sixth (?)	At least 4 months	None*	Spontaneous	Infant living	One normal pregnancy without chorea
5	19	Unmarried	1	0	0	1	None	Present	None	Present	Second	Seventh	Approx. 3 months	None*	Spontaneous (low forceps)	Infant living	None

* If other way possible the source was suggested in these patients

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DUCTLESS GLANDS

PAPILLARY ADENOCARCINOMA OF THE THYROID GLAND, SO-CALLED LATERAL ABERRANT THYROID TUMORS*

B. MARDEN BLACK

To verify further the accuracy of the belief at this institution that so-called lateral aberrant thyroid tumors are metastatic lesions from a primary papillary adenocarcinoma in the corresponding lobe of the thyroid gland and to evaluate our current methods of treatment, the records of all cases of proved papillary adenocarcinoma of the thyroid gland encountered at the Mayo Clinic from 1938 to 1945, inclusive, have been reviewed. All cases of carcinoma of the thyroid gland encountered here prior to 1938 were reviewed by Pemberton. Only those cases in which tissue was available for microscopic examination have been included in the present study.

In all, 112 cases were encountered in the eight years, 1938-1945, inclusive. Females outnumbered males in this series in the ratio of 2.6:1 whereas females outnumbered males in the ratio of 1.7:1 in the 774 cases of carcinoma of the thyroid gland reported by Pemberton. Our impression that patients who had papillary adenocarcinoma with massive involvement of lymph nodes were somewhat younger, as a group, than those who had papillary adenocarcinoma without involvement of lymph nodes was borne out in this study. The mean age of all patients in the series was 43.4 years. The mean age of patients with extensive metastatic lesions in the cervical lymph nodes was 25.9 years; two thirds of these patients were less than thirty years, and one third were less than twenty years of age at the time they were first seen here. The mean age of all patients with involvement of cervical lymph nodes was 35.2 years. In sixty-eight cases, no lymph nodes were involved while in forty-four cases involvement of the lymph nodes to a greater or less extent had developed. The number of lymph nodes involved varied from one to so many as to give the appearance of massive bilateral cervical involvement.

Previous Thyroidectomy or Biopsy.—Ten patients had undergone previous operations on the thyroid gland. In several cases the patients came to the Clinic because of local recurrence and in two of these, further resection was possible (figs. 44 and 45). In one case no further surgical treatment was considered necessary and in two cases, removal of involved lymph nodes was carried out. In one case operation was advised because of recurrent exophthalmic goiter, and a papillary adenocarcinoma was found in the resected thyroid. Fifteen patients had had involved lymph nodes removed before they were seen at the Clinic and the advice reportedly given

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to these patients concerning the necessity of further treatment reflects something of the confusion which exists generally regarding proper management of papillary adenocarcinoma of the thyroid gland. The patients had been correctly advised, presumably, in six cases, in that further operations had been proposed after biopsy. However, it was reported that in four cases irradiation only had been advised and in five cases no further treat-



Fig. 44—Huge recurrent papillary adenocarcinoma of the thyroid gland. No lymph nodes were involved.

ment of any type had been suggested. Thus in nine of the fifteen patients in whom the diagnosis was made after the removal of lymph nodes it appeared that inadequate treatment or no treatment had been carried out or advised.

Patients without Involvement of Lymph Nodes.—Of the sixty-eight patients without involvement of lymph nodes, eighteen had a palpable nodule in the thyroid gland which was not recognizable as malignant on

physical examination. In twenty-seven patients the lesion in the thyroid gland was considered malignant on clinical examination or was known to be malignant as evidenced by the findings at a former biopsy. In the remaining twenty-three patients, papillary adenocarcinoma was a chance finding. In



Fig 43.—Same case as in figure 44. Section shows typical papillary adenocarcinoma, grade 1 ($\times 130$).



Fig 46.—Minute papillary adenocarcinoma associated with exophthalmic goiter. The lesion was clinically insignificant and operation had been advised because of the associated exophthalmic goiter.

eleven of these twenty-three cases operation had been advised because of exophthalmic goiter, in six because of adenomatous goiter with hyperthyroidism and in six because of adenomatous goiter without hyperthyroidism.

The association of exophthalmic goiter and carcinoma of the thyroid gland is no longer regarded as particularly unusual (figs. 46 and 47). During the years covered in the present study this association was found once in every 234 cases of exophthalmic goiter in which operation was performed, and since 1907 at the Mayo Clinic, one case of carcinoma of the thyroid gland was found in association with exophthalmic goiter in approximately every 1,000 cases of exophthalmic goiter. The apparent increased incidence recently is to be explained probably by the fact that interest in the possible association of the two conditions has led to a more meticulous microscopic examination of the resected tissue in all cases of exophthalmic goiter.



Fig. 47.—Same case as figure 46. Section shows typical papillary adenocarcinoma, grade 1, as well as the surrounding thyroid tissue involved in diffuse parenchymatous hypertrophy ($\times 60$).

Patients with Involvement of Lymph Nodes.—Lymph nodes were involved in forty-four of the 112 cases. In eleven, the lymph nodes were not palpable clinically and in nine other cases, while both the primary tumor and the lymph nodes were palpable, the primary tumor was more prominent than the involved lymph nodes. In the remaining twenty-four cases, the primary lesion was either not palpable or if palpable, was not evident as malignant, while the involvement of lymph nodes was either extensive or far more evident than was the involvement of the lobe of the thyroid. In eight of the twenty-four cases, one or at most a few lymph nodes were

palpable while in sixteen cases numerous lymph nodes were involved, usually in several anatomic regions of the neck. Thus, in about half of the thirty-three cases in which lymph nodes were palpable and in about a third of the forty-four patients in this group, the lesions clinically were typical so-called lateral aberrant thyroid tumors (figs. 48 and 49).

Extent of Involvement of Lymph Nodes.—The deep jugular and paratracheal nodes were involved most often. Pretracheal and submaxillary lymph nodes were seldom involved; evidence of involvement of the lymph nodes of the submental group was not found. In each case the lobe of the thyroid on the same side as the involved lymph nodes harbored the primary lesion. When numerous lymph nodes on both sides of the neck were involved, there was usually extensive involvement of both lobes of the thyroid. When many nodes were involved on one side and only a few on the opposite side, the lobe of the thyroid on the same side as the extensive in-

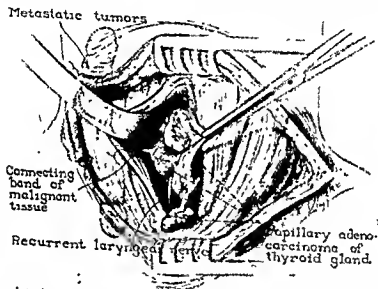


Fig. 48—Artist's conception of extent of papillary adenocarcinoma of thyroid gland in one case. The connecting band of malignant tissue is somewhat unusual.

volvement of lymph nodes was usually more extensively involved than the opposite lobe. When the involvement of lymph nodes was limited, the location of the involved lymph nodes often suggested the location of the primary lesion in the lobe of the thyroid gland. When the primary lesion was near the superior pole, the involved lymph nodes were usually in the superior deep jugular group, particularly the lowermost nodes of this group. When the primary lesion occupied a location deep in the lobe or near the inferior pole, the inferior deep jugular nodes were involved most frequently. In cases in which massive involvement of lymph nodes occurred, there was usually extensive involvement of the corresponding lobe of the thyroid. This was not invariable, however, and in some cases in which extensive involvement of lymph nodes occurred, the primary lesion was not evident even after exposure of the lobe, but was found only after microscopic study of the resected lobe of the thyroid.

Surgical Treatment. Extent of Removal of Thyroid Gland—In the present series of cases either total or subtotal removal of the involved lobe of the thyroid gland was carried out. In some cases the operation was limited to subtotal lobectomy because the carcinoma was so small that more extensive resection was not thought necessary. In other cases the carcinoma was not recognized as such until the patient had been taken from the operating room. In all, subtotal lobectomy, either on one or both sides, was carried out in sixty-four cases, in twenty-three of which the primary carcinoma was small and was found incidentally. However, among these sixty-four cases,



Fig. 49 —Same case as figure 48. Section illustrates typical papillary adenocarcinoma, grade 1 ($\times 13$).

recurrence in the remnant was known to have developed in five cases or in about 12 per cent of the forty-one cases in which clinically significant lesions were found. The fact that local recurrence is frequent after subtotal lobectomy is further emphasized by the fact that six of the ten patients who had had subtotal thyroidectomy or lobectomy before coming to the Clinic had had local recurrences. Another difficulty which was comparatively minor in nature, arose occasionally after subtotal operations. If a remnant sufficiently large to permit palpation had been left after partial lobectomy uncertainty always arose on subsequent examination as to whether the palpable thyroid tissue was remnant only or recurrent adenocarcinoma.

Local recurrence in a remnant can be prevented only by total lobectomy, which, in the absence of carcinomatous infiltration of the surrounding structures, is not particularly difficult. The usual method is to begin the separation of the lobe from the trachea at the inferior pole after the recurrent laryngeal nerve has been visualized and after the superior and inferior thyroid arteries and the isthmus have been divided. The dissection is continued cranially, further exposing the nerve as the lobe is being separated from the trachea. Early ligation of the superior and inferior thyroid arteries and division of the isthmus and suspensory ligaments will permit a comparatively bloodless dissection. In the present series bilateral total lobectomy was rarely found necessary and it was usually possible, after total lobectomy on the side more extensively involved, to limit the operation to subtotal lobectomy on the opposite side. Bilateral total lobectomy along with extensive removal of lymph nodes was rarely thought advisable as a single stage procedure.

Extent of Removal of Lymph Nodes.—The treatment in nine of the forty-four cases in which the lymph nodes were involved was considered palliative. In nine of the remaining thirty-five cases, further involvement of lymph nodes became apparent after the original operation, and removal of these lymph nodes was necessary at a subsequent operation. These secondary operations were frequently limited, and rarely was the removal of more than single anatomic groups of nodes necessary. The cosmetic result after such limited operations was far more satisfactory than that following block dissections. In view of the number of young women with extensive involvement of lymph nodes in the series discussed herein, consideration of the cosmetic result was of some importance. As previously stated, with papillary lesions the grade of malignancy is so low and the metastatic carcinomas tend to be confined to the nodes so long that block cervical dissections can be avoided usually. In a few cases in this series, however, the involvement of lymph nodes was so extensive that block cervical dissections were carried out.

COMMENT AND SUMMARY

The findings in this review of the 112 cases of papillary adenocarcinomas of the thyroid gland encountered at the Mayo Clinic in recent years have served to strengthen the belief, held here for many years, that the lateral cervical papillary tumors are metastatic lesions from a primary papillary adenocarcinoma of the thyroid gland. The conflicting views concerning these tumors, particularly as to whether they are benign or malignant and as to whether there is always a malignant lesion in the thyroid gland in such cases, have led to evident confusion as to proper management of such lesions. Thus, in almost two thirds of the cases in the small group in which one of the metastatic lesions had been removed at biopsy elsewhere, removal of the primary lesion had not been advised. The evident lack of understanding generally of the so-called lateral aberrant thyroid tumors would be dispelled, it seems, if their metastatic nature were widely recognized.

The malignant nature of the primary lesion in the thyroid gland is well illustrated by the fact that a number of local recurrences follow subtotal lobectomy. It can probably be stated definitely that if the papillary adeno-

carcinoma is larger than a few millimeters in diameter, and if it is recognized during the operation, a total rather than a subtotal lobectomy should be carried out. In spite of the fact that subsequent operations to remove involved cervical lymph nodes were not infrequently necessary, I still believe that the removal of only the involved lymph nodes, generally as a group, is sufficiently radical treatment of the metastatic lesions. Careful examination at stated intervals after the operation to determine whether unremoved lymph nodes have become palpable is, of course, necessary.

In addition to the fact that a primary papillary adenocarcinoma was found in every case in the series, the fact that the primary lesion was always present in the corresponding lobe of the thyroid gland is of importance from the standpoint of treatment. While no contralateral metastatic lesions were observed, involved lymph nodes were found in the opposite lateral cervical region in two cases in which the primary adenocarcinoma involved one lobe and only the isthmus on the opposite side.

THE USE OF RADIOIODINE IN THE STUDY AND TREATMENT OF THYROID DISEASE*

F. RAYMOND KEATING, JR

Radioiodine has proved to be a useful tool for the study of problems related to thyroid function both in animals and in human beings. It also has been used in the treatment of hyperthyroidism with some success but it is far too early to evaluate thoroughly the usefulness and limitations of this form of treatment. The possibilities of treating malignancy of the thyroid with radioiodine are very disappointing, since it appears probable that only in exceptional cases will this lesion prove amenable to such treatment. The use of radioiodine is hazardous because of the danger of radiation effects. The possibility of serious delayed effects of radiation requires careful consideration when radioiodine is employed for the treatment of non-malignant disease.

A PRELIMINARY APPRAISAL OF RADIOIODINE TRACERS IN MAN: THE SIGNIFICANCE OF URINARY EXCRETION OF RADIOIODINE†

F. RAYMOND KEATING, JR., MARSCHELLE H. POWER, JOSEPH BERKSON AND SAMUEL T. HAINES

Radioiodine and natural iodine are chemically and physiologically identical, providing the former is present in quantities so small as to be without biologic effects due to radiation per se. A minute quantity of

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† Abstract of paper published in full in the *Transactions of the American Association for the Study of Goiter*. (In press)

radioiodine may be used to trace, by its radioactivity, the course of a given quantity of iodine through various chemical and biologic reactions. Hertz was the first to call attention to the unique possibilities of this method in the study of thyroid function and the first to apply it in experimental and clinical studies. Radioiodine tracers have subsequently been utilized in many studies dealing with the thyroid of laboratory animals, in vitro experiments and clinical investigations. The method has been applied to the study of the biosynthesis of thyroid hormone, the action of thyrotrophic hormone, the action of goitrogens and of other factors influencing the function of the thyroid, the functional activity of various thyroid tumors and a number of other problems.

The present study was undertaken to investigate the dynamics of iodine metabolism by the tracer method, and to determine, if possible, the rate at which radioiodine is collected by the thyroid, disappears from the blood and is excreted in the urine. The study was undertaken in the hope that this approach might provide the tracer method with greater precision when applied to various aspects of thyroid function in man. A summary of the results follows.

The urinary excretion of radioiodine following its oral administration has been studied in normal subjects, euthyroid patients who had low-grade thyroid malignant lesions, patients who had myxedema and patients who had untreated exophthalmic goiter.

The urinary excretion curves differ significantly among the euthyroid, hypothyroid and hyperthyroid groups. Mathematical analysis of the urinary excretion yields the following four quantities: (1) the renal fraction (which is the fraction of the dose of radioiodine primarily excreted in the urine); (2) the disappearance rate (which is the proportional rate of disappearance of radioiodine from the blood); (3) the renal excretion rate (which is the proportional rate of excretion into the urine), and (4) the collection rate (which measures the proportional rate of disappearance into other sites than the kidneys). In so far as the thyroid represents the chief site in the body for collecting iodine, the last of these four values serves as an index of thyroid collection rate. When the radioiodine curve of the thyroid can be determined by observations obtained from the subject's thyroid directly, the true rate of collection by the thyroid can be estimated.

Estimations of disappearance rate, based on analysis of renal excretion, have been found to agree fairly closely with estimations of the same quantity based on direct measurements of blood samples, measurements of the thyroid in vivo and measurements of peripheral radioactivity in vivo.

The renal fraction is greater than normal in hypothyroid patients and is less than normal in hyperthyroid patients. The disappearance rate is less in hypothyroid patients than in normal subjects and is markedly greater than normal in cases of hyperthyroidism. Significant individual variations occur in renal excretion rates but no significant differences were observed in the mean renal excretion rates among the four groups of cases studied. The most significant variation observed occurred in the collection rates, which were very much less than normal in the hypothyroid cases, and averaged six times the normal in the hyperthyroid patients.

SURGICAL ASPECTS OF HYPERPARATHYROIDISM: REVIEW OF SIXTY-THREE CASES*

R. MARDEN BLACK

Sixty-three patients with proved hyperparathyroidism were observed at the Mayo Clinic through 1946. The disease was due to a single adenoma in fifty-six cases, to multiple adenomas in three cases, and to diffuse primary hyperplasia in four cases. The ages of the patients ranged from the second to the seventh decade. Complications of the urinary tract were more common and more important than osseous complications. The diagnosis was established with certainty in three cases in the absence of any complications, on the basis of the characteristic changes in the content of calcium and phosphorus in the blood and urine. Since the diagnosis can be made with complete certainty, exploration of the parathyroid glands is never indicated in an effort to establish the diagnosis, and the surgeon must accept the fact that in every case of hyperparathyroidism one adenoma or more or primary hyperplasia is present.

The treatment of hyperparathyroidism is surgical. Adenomas should be removed completely and, in cases of diffuse primary hyperplasia, the hyperplastic tissue should be excised subtotally, with the preservation of between 30 and 200 mg. of hyperplastic tissue. In more than 80 per cent of cases, the abnormal tissue may be found by dissection under direct vision through a cervical incision (cervical and posterior superior mediastinal dissection). A second operation, through a sternotomy incision, will be necessary in the remaining cases (anterior superior mediastinal dissection). Secondary dissection is more difficult and far less certain than primary dissection, so that every effort should be made at complete operation, both in the identification of the parathyroid glands present and in the designation of those missing, at the first cervical dissection.

RESULTS OF ADMINISTRATION OF ANTERIOR PITUITARY ADRENOCORTICOTROPIC HORMONE TO A NORMAL HUMAN SUBJECT†

HAROLD L. MASON, MARSCHELLE M. POWER, EDWARD H. RYNEARSON,
LETIZIA C. CIARAMELLI, CHOH HAO LI AND HERBERT M. EVANS

When 100 mg. of the anterior hypophyseal adrenocorticotrophic hormone was administered daily, in divided doses, to a normal young woman it caused an increased excretion of urinary steroids, which is evidence of stimulation of adrenocortical function. The daily excretion of 17-ketosteroids increased from 4.84 to 15.5 mg. and that of the cortin-like substances increased from 0.180 to 1.44 mg. Development of acne and a de-

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† Abstract of paper published in full in *The Journal of Clinical Endocrinology*, 8:1-14 (Jan.) 1948.

crease in the excretion of creatine suggested that the production of androgens was increased. The excretion of pregnanediol, estrogens and gonadotrophin was not affected measurably. Androsterone and etiocholanolone were isolated from the urine in increased amounts during the period when ACTH was being administered. The amount of pregnanediol that could be isolated was unchanged by administration of the hormone. The amount of cholesterol that was isolated from the urine was decreased during the period of administration of the hormone.

Electrolyte metabolism appeared to be essentially undisturbed by the hormone as judged by the concentration of sodium, potassium, chloride and phosphorus in the blood and urine. There was a small but apparently significant increase in the carbon dioxide content of the plasma.

The value for the urinary nitrogen increased but the increase was so small that it could not be attributed with certainty to administration of the hormone.

The value for the free cholesterol of the plasma decreased significantly. There was no change in the quantity of the blood proteins or in their quality as determined by electrophoresis. The value for the serum alkaline phosphatase remained unchanged. Anemia developed but the erythrocyte and leukocyte counts were not affected significantly.

Tolerance to glucose was not affected measurably but some resistance to insulin developed.

THYMECTOMY IN THE TREATMENT OF MYASTHENIA GRAVIS: REPORT BASED ON THIRTY-TWO CASES*

L. M. EATON, O. THERON CLAGETT, C. ALLEN GOOD AND JOHN R. McDONALD

One of us (Eaton) previously summarized the evidence for the relationship between myasthenia gravis and the thymus gland. The surgeons did not await the final solution of the problem before attempting to cure patients by removal of the thymus gland. The first surgical efforts, made before satisfactory medical treatment was available and before the technique of thoracic surgery had advanced to its present status, were failures. With the report of Blalock, Mason, Morgan and Riven in 1939 of apparent success in the treatment of myasthenia gravis by removal of a tumor from the anterior part of the mediastinum, which tumor, although not histologically verified, was almost certainly of thymic origin, our interest and that of other investigators was aroused. After hearing the report by Campbell, Fradkin and Lipetz at the meeting of the American Neurologic Association in 1941, our colleagues in the Department of Neurology and we decided to study intensely the problem of myasthenia gravis and its relationship to the thymus gland. We were soon rewarded by finding roentgenologic evidence of a large tumor in the mediastinum of a patient who had myasthenia gravis. Remission of the disease took place after roentgenologic irradiation

* Abridgment of paper submitted to the Archives of Neurology and Psychiatry.

of the tumor, and on December 20, 1941, the tumor was removed surgically by one of us (Clagett). The thymic origin of the tumor was verified histologically.

In 1941 one of us (Good) became interested in the roentgenologic aspects of the problem and undertook a study of our cases of myasthenia gravis. In a study of 206 consecutive cases of myasthenia gravis a diagnosis of thymic tumor has been made by roentgenologic methods in thirty-three cases. The accuracy of the roentgenologic diagnosis has been verified surgically in twenty cases and at necropsy in four cases. In only one instance did operation fail to verify the presence of a thymic tumor in this group of thirty-three cases. In the remaining eight cases the roentgenologic evidence of an anterior mediastinal mass was unequivocal, but the opportunity for verification at operation or necropsy has not arisen. Of the 173 patients in whom roentgenologic evidence of thymic tumor was lacking, twenty-five have undergone surgical exploration and three have been studied at necropsy; in none was a thymic tumor found.

Thus, we can conclude that careful roentgenologic examination will reveal evidence of thymic tumor in approximately 15 per cent of patients who have myasthenia gravis (thirty-two of 206).

There is reason to believe that this percentage approaches the actual frequency of occurrence of thymic tumor among patients who have myasthenia gravis. The incidence of thymic tumor at necropsy in the reported cases of myasthenia gravis is higher and probably less accurate than the incidence established by roentgenologic examination, since there has been a tendency to report those cases in which a tumor actually was found.

Our experience would lead us to believe that the true incidence of thymic tumor among patients who have myasthenia gravis is probably not significantly greater than the incidence of 15.5 per cent detected by our roentgenologists. That necropsy reports may be misleading is attested to by our records. Seventeen complete necropsy studies of myasthenia gravis have been made at the Mayo Clinic. Thymic tumors were present in nine cases, but in two of the nine cases necropsy had been performed subsequent to removal of the tumor, and in at least three other cases the patients came to us in a critical condition for consideration of surgical removal of tumors of the thymus gland which had been found to be present by previous roentgenologic examination. Thus, a much higher incidence of thymic tumor at necropsy is found in our series than would normally occur.

Last, the 15.5 per cent incidence of tumors of the thymus gland as demonstrated roentgenologically in our group of 206 cases of myasthenia gravis agrees well with the 13.9 per cent incidence of thymic tumors found during thymectomy in eighty-six cases from the literature (Blalock: two tumors in twenty cases; Viets: four tumors in fifteen cases; Keynes: six tumors in fifty-one cases), in which no attempt was made to select the patients on the basis of whether or not there was roentgenologic evidence of thymic tumor.

Although in our series of 206 patients with myasthenia gravis forty-six have been subjected to operation for removal of the thymus gland, we shall confine the analysis of results to the thirty-two who were operated on between December 20, 1941, and September 7, 1945. Thus are included only

patients whose condition had been followed for at least six months on June 1, 1946, when the data regarding the results were assembled.

EVALUATION OF RESULTS

Introduction.—In spite of experience gained from a specific interest in myasthenia gravis and in caring for many myasthenic patients, we are unable to predict with certainty the course of the disease in any particular case. Of course, predictions can be made roughly; but their accuracy is limited sufficiently that we cannot say that a particular patient who has experienced marked remission of his symptoms of myasthenia gravis after thymectomy might not have experienced the remission spontaneously.

Realization of the fact that the course of myasthenia gravis is extremely variable has forced us to conclude that the results in this group of thirty-two cases furnishes no conclusive evidence as to the value of thymectomy in the treatment of this disease. In spite of this, we trust that a report at this time is of value from the standpoint of indicating an apparent trend in the response of myasthenic patients to thymectomy and in presenting knowledge gleaned from operative and postoperative experience with these patients and from pathologic study of the tissues removed.

Analysis of Results.—There were fifteen cases of thymoma in this group of thirty-two cases. The large number of patients who had thymomas is accounted for by the fact that early in this study only patients with roentgenologic evidence of an anterior mediastinal tumor were advised to undergo surgical treatment. Later in the course of the study, thymectomy was offered to the myasthenic patient as a possible means of influencing favorably the fundamental course of the disease. The same advice is given such patients at the present time. Consequently, the proportion of cases of thymoma has decreased precipitously.

One patient who had a thymoma died on the third day after operation when she suddenly stopped breathing after the exertion entailed by the administration of an enema.

Only three patients who had thymomas were unimproved at the time the evaluation was made. One patient was less well than before operation; the other two were somewhat better subjectively.

Four patients who had thymomas were moderately better. This classification of results is limited to those patients who, at the time this study was completed, were not only better subjectively but who could substantiate their claim of improvement by demonstrating that they could be as active as formerly on a significantly reduced intake of neostigmine or that they could do substantially more work on the same amount of neostigmine.

Seven patients in this group of fifteen with thymomas were classified as considerably improved. In this category are grouped those patients who, at the time this study was completed, had completely recovered or who were able to live normally and could maintain themselves on a greatly reduced amount of neostigmine.

The thymomas in three cases were inoperable because they had either invaded such neighboring structures as the innominate vein and lung or had implanted themselves widely on the pleural surfaces.

It is of interest to notice the age and sex of the patients who had thymomas. There were eleven males and four females. The ages ranged from

in the stage of immediate postoperative convalescence. He was a man sixty-seven years old who ordinarily would not have undergone surgical treatment had there not been a mistaken diagnosis of "thymic tumor" by the roentgenologist. However, this case represents the only roentgenologic error in the diagnosis of thymic tumor thus far detected in our series. In this particular case an insignificant amount of thymic tissue was discovered. The same is true in another case, and consequently the failure of this patient to improve is understandable.

So far as we can ascertain, no patients aside from those who died a few days after operation have been made worse by operation. The two patients who died three and six months after operation were not helped, and their symptoms, which had been steadily progressing in severity, continued to progress.

An analysis of these records fails to show any significant correlation between the duration of symptoms of myasthenia gravis at the time of operation and the result obtained by removal of the thymus gland. That a long duration of the illness is not a contraindication to thymectomy is demonstrated by the good results obtained in two cases, in which the onset dated back to nine and six years before operation. Furthermore, there seems to be no significant correlation between the response to thymectomy and the length of time that neostigmine had been used in treatment.

We are unable to make any definite correlation between the result of operation and the pathologic observations except that the group who had thymomas as a whole have done better than the group who did not have thymomas. Histologic evidence of thymic hyperplasia was present in four of eight patients who did not improve after thymectomy (no tumor), whereas in only four of the eight patients showing improvement was there evidence of hyperplasia. This aspect of the problem will be discussed in more detail under the heading of "Pathologic aspects."

In three cases it is of interest to note that the patients laid considerable emphasis on the fact that they had lost their sense of taste for periods up to several months during the course of their illness. This has been an important complaint of three other patients not included in this series, two with unequivocal roentgenologic evidence of thymoma. The significance, if any, of this complaint in myasthenia gravis is unknown to us.

SURGICAL ASPECTS

Selection of Patients for Surgical Treatment.—All myasthenic patients presenting definite roentgenologic evidence of thymic tumor have been advised to undergo operation unless two contraindications were present: (1) definite clinical and roentgenologic evidence that the tumor has implanted itself widely within the thoracic cage (one case); and (2) clinical evidence that the condition of the patient is such as to make the risk of surgical exploration unreasonably excessive. Patients without roentgenologic evidence of tumor have not been urged to undergo thymectomy. The experimental nature of the procedure has been explained carefully and the patient has been offered thymectomy as a procedure which may possibly influence the fundamental course of his or her disease beneficially. Naturally, those who have milder degrees of myasthenia gravis, particularly if the course is not a progressive one, are seldom interested in surgical treatment.

Preoperative Treatment.—The patient usually is placed in the hospital for two or three days before operation, where he will not be exposed to respiratory infections. Penicillin is administered for a day or two preceding operation. The patient is kept at rest and the optimal dosage of neostigmine and ephedrine is administered. Natural fluctuations in the severity of the disease are taken into account and surgical operation is performed when the patient is at his best. For instance, since in the female the symptoms of myasthenia gravis tend to be more intense during the week or two preceding the onset of the menses, operation is postponed until this period has passed. It is carried out during the first two weeks of the menstrual cycle, when the patient is at her best. If a patient's condition is such as to make the risk of operation excessive, we have resorted to roentgen-ray irradiation of the thymic area in an effort to secure a remission, at which time, if remission is obtained, surgery can be undertaken with less risk.

Operation.—A variety of surgical approaches to the thymic tumors have been used. Occasionally, the tumor has been approached posterolaterally after resection of a rib. At other times, when the tumor presented itself to one side or the other of the sternum, the tumor has been removed after resection of the costal cartilages on that side. Although these two approaches often are advantageous from the standpoint of removal of the tumor, they do not allow for removal of other thymic tissue which may be present. At present, we agree with Blalock that the preferred surgical approach is obtained by splitting the sternum.

During the operation, which usually requires thirty to fifty minutes, neostigmine methylsulfate may be administered parenterally. As a rule, however, the preoperative dose of 0.5 to 1.5 mg. neostigmine methylsulfate is sufficient.

The anesthetic agent preferred is a combination of nitrous oxide, oxygen and ether. An intratracheal tube is inserted routinely for administration of the agent.

Postoperative Treatment.—Postoperatively, the patients are placed in an oxygen tent. They receive neostigmine methylsulfate parenterally every two to three hours or oftener, as required. A half to 1.5 mg. usually is used at each dose, depending on the patient's response. Ephedrine and atropine frequently are administered concomitantly.

It is of utmost importance that a clear airway be maintained. If needed, a mechanical aspirator should be on hand for removal of secretions from the pharynx. Splendid co-operation from anesthetists and bronchoscopists has been obtained; the results of maintenance of a clear airway by means of bronchoscopic aspiration have been important, since they have enabled several of our patients to survive the immediate postoperative course.

As a rule, use of the oxygen tent and the parenteral administration of neostigmine can be discontinued on the second or third day after operation. The patient then takes orally whatever medication is required.

The importance of a Drinker type of respirator cannot be overemphasized. Its use has been of exceptional importance in several cases. If oxygenation is inadequate, the patients become apprehensive and exhaust themselves. The improvement in the condition of several patients has been phenomenal after rest was secured by placing of the patient in the respirator, removal of inspissated material from the trachea and bronchi by means

of the bronchoscope, and by the administration of morphine sulfate, which otherwise must be used sparingly in these cases.

In the average case the patient is allowed to be out of bed on the fourth or fifth day, and to leave the hospital seven to ten days after operation. Only two patients of this series required hospital care longer than two weeks.

Röntgen-ray irradiation of the thymic area has been used postoperatively in those cases in which there was not reasonable assurance that all thymic tissue had been removed.

On dismissal from the hospital, the patient is instructed to resume normal activities and to reduce his medication as rapidly as his condition warrants.

PATHOLOGIC ASPECTS

Up to the present, we have been unable to demonstrate that any curare-like substance is present in extracts of thymomas. In three cases, both physiologic saline extracts and alcohol extracts were prepared by Doctor Mason. Doctor Bollman injected these extracts into mice and failed to detect any myasthenic-like effect. It is possible that future investigations with more sensitive technics will lead to positive results.

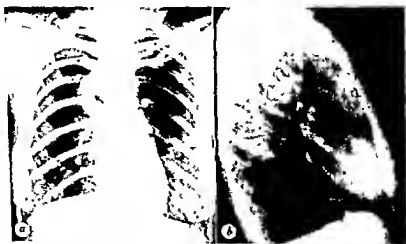


Fig. 51 —*a*, Thymoma projecting to the right of the sternum; *b*, lateral view of the same lesion, showing the thymoma in the anterior part of the mediastinum.

The thymomas varied from a size of 2.5 by 3.5 by 2 cm. and a weight of 12 gm., to a size of 15 by 12 by 6 cm. and a weight of 462 gm. Four of the tumors were cystic and six contained varying amounts of calcium. Six were found, at operation, to have invaded surrounding structures (figs. 51 and 52) and three were inoperable, only specimens for biopsy having been removed. Histologic examination failed to show any essential differences between those lesions which were invasive and those which were not. Four of the tumors showed varying degrees of necrosis. In one case, the central seven-eighths of the tumor was necrotic. The necrosis may well have resulted from rather intensive roentgen-ray irradiation administered in four

courses, the first almost three years and the last seven months before operation



Fig 52.—Same case as in figure 51. Direct extension of tissue of the thymoma into the wall of the vena cava (hematoxylin and eosin $\times 100$).

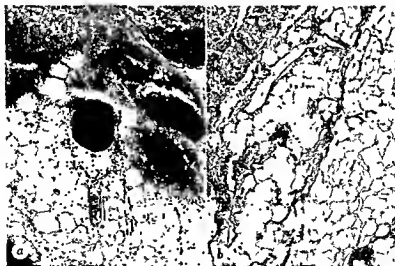


Fig 53.—*a*, Thymic hyperplasia, this gland was considered to be hyperplastic, since the patient was forty years old (hematoxylin and eosin $\times 100$); *b*, nonhyperplastic thymus gland, the gland was composed of 99 per cent fat and 10 per cent thymic tissue (hematoxylin and eosin $\times 100$).

One of us (McDonald) has studied these tumors and thymus glands intensively, and with Doctor Murray has published one report of them,

These tumors were found to be composed of two types of cells. One type, the thymocytic type, is identical with the small lymphocyte seen in lymph nodes. The other is oval, about three or four times as large as a lymphocyte, and contains a faint acidophilic cytoplasm. The nucleus of this oval type stains lightly with hematoxylin. This cell is morphologically indistinguishable from the very young cells which line minute capillaries. The origin of this particular cell is questionable, and in this report it is designated as "epithelial-like cell." The proportion of thymocytic and epithelial-like cells varied widely from case to case. In four cases the thymocytic cells were estimated to compose as much as 95 per cent of the tumor, whereas in one other case, the epithelial-like cell was predominant to the same degree. In the rest of the tumors varying proportions of the two cell types, between these extremes, occurred.

In spite of careful study of the subject, we have found it extremely difficult to state with certainty whether or not a given thymus gland removed at operation is hyperplastic (fig. 53). Obviously, the weight of tissue removed at operation is not an adequate criterion, since the amount of fat and fibrous tissue therein varies greatly. At present, the determination of hyperplasia depends on the following factors: (1) the amount of tissue present, (2) the proportions of thymic and fat tissue in the mass, and (3) the age of the patient. The latter point is important, since it is known that the adipose connective tissue is found to increase and the thymic tissue to decrease in progressive age groups.

SUMMARY AND CONCLUSIONS

The pathologists have accumulated convincing evidence that there is some relationship between myasthenia gravis and the condition of the thymus gland.

Proper roentgenologic technic reveals evidence of thymic tumor in approximately 15 per cent of patients who have myasthenia gravis. Evidence has been presented to substantiate the claim that this figure closely approximates the true incidence of thymic tumor in this disease.

An analysis of the results obtained for fifteen patients who had myasthenia gravis and associated thymic tumor and seventeen patients without thymic tumor who underwent operation for removal of the thymus gland shows that 60 per cent of patients were improved four and a half years to a half year after operation. Although these results are encouraging, they must not be looked on as conclusive evidence that thymectomy is of value in the treatment of myasthenia gravis, since the course of myasthenia gravis cannot be predicted with sufficient certainty to make it possible to say that remission would not have taken place spontaneously in these cases.

At least, in certain cases in which myasthenia gravis is associated with thymic tumor, the tumor is present before the onset of the symptoms of myasthenia gravis.

On the basis of this study it would seem that roentgen-ray irradiation of the thymus gland may be of value in treatment.

At present, no significant correlation can be made between the result obtained and the duration of the disease, the length of preoperative treatment with neostigmine or the histologic observations made in a study of the thymic tissue removed.

The problem of determination of whether a thymus gland removed at operation is or is not hyperplastic is not a static one. Such designations must be considered tentative at this time.

A conclusive opinion as to the value of thymectomy in myasthenia gravis awaits the careful study of a larger number of cases over a longer period of time, and comparison of the course in the group of patients treated surgically with the course of a control group of patients receiving medical treatment only.

RELATION OF URINARY STEROIDS TO THE DIAGNOSIS OF ADRENAL CORTICAL TUMORS AND ADRENAL CORTICAL HYPERPLASIA: QUANTITATIVE AND ISOLATION STUDIES*

EDWIN J. KEPLER AND HAROLD L. MASON

The urinary 17-ketosteroids and the 3(β)-alcoholic fraction of the 17-ketosteroids were determined in six cases of adrenal cortical tumor and five cases of cortical hyperplasia. The ketonic and nonketonic steroids were isolated from the urine in six cases of tumor and four of hyperplasia.

In one case of tumor the quantitative determination of 17-ketosteroids gave a result below the normal range of values. In another case, the 3(β)-alcoholic fraction was only 7.5 per cent of the total 17-ketosteroids (30 mg.). In the four other cases of tumor the 3(β)-alcoholic fraction was 48 to 77 per cent of the total amounts (68 to 1,005 mg.) of 17-ketosteroids. In cases of hyperplasia the 3(β)-alcoholic fraction was 2 to 20 per cent of the total 17-ketosteroids (10 to 123 mg.). Consideration of these results in conjunction with those of other investigators indicates that excretion of 50 mg. or more of 17-ketosteroids per day with a 3(β)-alcoholic fraction of 50 per cent or more is strong evidence in favor of the presence of adrenal tumor. In a few instances, however, an adrenal tumor may be present when these values are considerably lower and within the range of values which have been found in association with cortical hyperplasia.

The results of the isolation studies emphasize again the relatively large amounts of dehydroisoandrosterone which are excreted in cases of adrenal tumor. Very little of this substance was isolated in the cases of hyperplasia. Androsterone and etiocholan-3(α)-ol-17-one were isolated, the latter more consistently in the cases of tumor, the former in all cases of hyperplasia. Pregnane-3(α), 20(α)-diol was isolated in all cases of tumor and in three cases of hyperplasia. Pregnane-3(β), 20(α)-diol was tentatively identified in two cases of hyperplasia. Pregnane-3(α), 17, 20-triol was found in one case of tumor and in three cases of hyperplasia. A new 17-ketosteroid, androstane-3(α), 11-diol-17-one, was isolated in three cases of tumor and in all of the cases of hyperplasia. It appears to be related to the 11-oxygen-

* Abstract of paper published in full in *The Journal of Clinical Endocrinology*, 7:543-558 (Aug) 1947.

ated adrenal hormones. Excessive excretion of estrogens was observed in only one case (of tumor) and estrone was isolated from the urine in this case.

Pregnane-3 α ,17,20-triol appears to be found more often in association with cortical hyperplasia than with tumors. Examination of the urine for this substance may well be of value for confirmation of a diagnosis of cortical hyperplasia.

Finally, our observations, taken in conjunction with others reported in the literature, indicate that every patient presenting symptoms suggesting adrenal cortical tumor or adrenal cortical hyperplasia must be studied individually, using both clinical and laboratory procedures. Neither is self-sufficient.

EFFECTS OF SYNTHETIC 11-DEHYDROCORTICOSTERONE (COMPOUND A) IN A SUBJECT WITH ADDISON'S DISEASE*

RANDALL G. SPRAGUE, CLIFFORD F. GASTINEAU, HAROLD L. MASON AND
MARSCHELLE H. POWER

A study of the effects of synthetic 11-dehydrocorticosterone (both the acetate and the free compound) on a patient with Addison's disease was carried out. Doses from 50 to 200 mg. daily were employed. The effects of 17-hydroxy-11-dehydrocorticosterone in a dose of 20 mg. daily were also studied.

After a period of administration of 11-dehydrocorticosterone acetate in a dose of 200 mg. daily there was a decrease in the urinary excretion of sodium chloride and water, a gain of body weight due to edema, a slight rise in blood pressure and an increase in cardiac size. There was also a decrease in urinary excretion of salt and water during a period of administration of 100 mg. of free 11-dehydrocorticosterone daily.

Effects of 11-dehydrocorticosterone on carbohydrate metabolism, studied by means of determinations of the fasting blood sugar, glucose and insulin tolerance tests, changes in the blood sugar during prolonged fasting and estimations of urinary nitrogen, were slight and in most instances of questionable significance.

The administration of 17-hydroxy-11-dehydrocorticosterone in a dose of 20 mg. daily resulted in a transient increase in the urinary excretion of sodium chloride. The compound in this dose had slight carbohydrate effects, as indicated by a diminished hypoglycemic response to insulin and better maintenance of the blood sugar level during fasting.

Both 11-dehydrocorticosterone and 17-hydroxy-11-dehydrocorticosterone produced increases in the urinary excretion of "cortin-like" substances in the urine. Neither produced any change in the urinary excretion of 17-ketosteroids.

Neither compound produced consistent changes in blood lipoids, serum proteins, albumin-globulin ratio or urinary phosphorus.

* Abstract of paper published in full in the *American Journal of Medicine*, 4, 175-185 (Feb.) 1949.

CUSHING'S DISEASE: A PRIMARY DISORDER OF THE ADRENAL CORTICES*

EDWIN J KEPLER

My subject, Cushing's disease, was selected with the hope that it might appeal to the experimentalist as well as to the clinician who is interested in endocrinology. By necessity I shall draw heavily from my own personal experience, which, because of my position, has been relatively extensive. It is necessary to use the word "relative" because Cushing's disease occurs infrequently and consequently no one person ever has the opportunity to study a large series of cases. Its incidence is not known. In the larger cities, patients afflicted with it occasionally may be seen on the streets and in public places. In smaller communities, it is distinctly a rarity. For example, in the twenty odd years that I have lived in Rochester, Minnesota, a town of about 35,000 people, to my knowledge not a single case has appeared locally.

RECENTLY ACQUIRED CLINICAL DATA†

The lack of any specific medical treatment, the uncertain response to roentgen therapy to the pituitary body and the miserable prognosis that confronts many of these patients led Dr. Walters and me a number of years ago to attempt to treat a few patients with Cushing's disease surgically. Generally less than half of each adrenal gland was removed. The therapeutic results were not impressive.

Subsequently, as it became apparent that the symptoms might well be an expression of adrenal cortical hyperfunction, my associates and I decided that if more adrenal tissue were removed the results might be better. For a time we considered seriously the advisability of performing total adrenalectomy. Ultimately we decided, however, to resort to a less radical procedure, feeling that there was a reasonable chance that subtotal bilateral adrenalectomy might be equally as effective and at the same time be less hazardous to the patient.

In the last three years four patients have been selected for this type of therapy. In three all of one adrenal gland was removed and subsequently about two thirds of the other, in a fourth about 60 per cent of each adrenal gland was removed.

The postoperative course in each instance was almost identical in character and I shall describe it here in considerable detail. Two digressions are indicated.

The first digression concerns the patients. All four, of whom three were women and one was a man, had the classic Cushing's syndrome in its worst form. One patient, the man, had congestive heart failure and was edematous to the waist line. All had severe hypertension. In none of the cases was the urinary excretion of 17-ketosteroids significantly increased. One patient at the second operation was found unexpectedly to have a low-

* Abstract of paper published as full in *The Annals of the New York Academy of Sciences*. (In press.)

† This material was presented in September, 1946, at the Laurentian Hormone Conference.

grade adrenal carcinoma about 1 inch (2.5 cm.) in diameter. We have reasons to believe that this carcinoma may not have been hyperfunctioning.

The second digression has to do with the ordinary sequence of events which occurs when a hyperfunctioning adrenal tumor is removed on one side and the opposite gland is either atrophic or functionally inadequate. If the patient has not been properly prepared, there develops, during the first twenty-four hours or shortly thereafter, because of transient, contra-adrenal cortical atrophy, a shocklike condition which is often fatal. The temperature rises to hyperpyrexial levels and the clinical picture resembles fulminating adrenal cortical insufficiency. If by virtue of treatment the patient does not die, improvement generally proceeds rapidly and at the end of a week or more it is obvious that he will recover. Three months after the operation many of the symptoms will have disappeared and ultimately, provided that there has been no recurrence of the tumor, the diagnostic signs of the former malady will have regressed completely. If all adrenal cortical tissue is removed, as seemed to be true in the case of Bartels of the Lahey Clinic, in which a nonfunctioning tumor was removed, presumably arising from a solitary adrenal gland, ordinary Addison's disease seems to follow. In his case, immediately after the operation the classic picture of postoperative adrenal insufficiency developed. With treatment the patient, a woman, recovered. When treatment was reduced or discontinued, adrenal insufficiency recurred. Soon it became apparent that continuous replacement therapy would be necessary. At the end of three months she was deeply pigmented and had all the other characteristic signs and symptoms of Addison's disease.

Let us return then to the postoperative course in the four cases under discussion. With these an entirely different sequence of events occurred, a picture of which we shall try to present in a composite form. Immediately after partial removal of the second adrenal gland nothing of any particular moment happened. Convalescence seemed to proceed uneventfully. Some time during the first week after operation or shortly thereafter the patients complained of nausea. They lost their appetite and vomited. The anorexia became more and more intense until finally they refused almost all food. Even the sight of food became repulsive. About the same time abdominal pain and tenderness made their appearance. Gradually the chemical composition of the blood became disordered. This disturbance generally was characterized, when the patient was not being treated with adrenocortical extract or electrolytes, by low concentrations of both sodium and potassium. The values for blood urea, and, as time went on, the concentration of blood calcium, slowly tended to rise and eventually attained levels seen in hyperparathyroidism. Phosphate levels, however, were not depressed.

Little by little the patients lost their "Cushingoid" appearance. The plethora faded and the skin became pallid. Striations disappeared, ecchymoses no longer occurred after venipuncture and it became possible to take the blood pressure without the production of petechiae. Imperceptibly, the hirsutism of the women vanished, so that the extremities became almost hairless. Growth of axillary hair was retarded. In every case the urinary excretion of 17-ketosteroids declined until it reached levels characteristic of Addison's disease. The blood pressure varied but in each

instance hypertensive values were obtained on most days irrespective of treatment. In one case administration of sodium chloride and sodium bicarbonate was followed by a sharp rise in blood pressure. Differential blood counts disclosed a gradual increase of the percentage of lymphocytes.

One of the patients, the man, seemingly was cured. Prior to the operations, his condition was the worst of the group. Two months after his second operation he was able to leave the hospital. By this time his condition was beginning to improve. During the next nine months the man was seen on two occasions and at each visit fairly complete examinations did not reveal

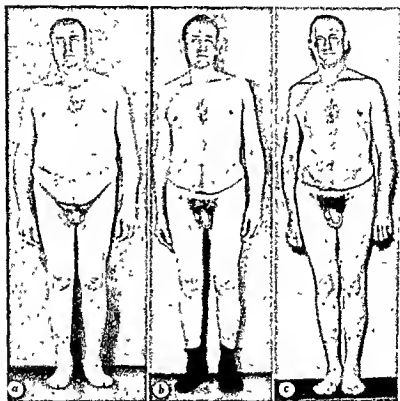


Fig 54.—Cushing's syndrome not associated with adrenal cortical tumor: *a*, appearance of patient before bilateral subtotal adrenalectomy; *b*, appearance of patient 6 months later; *c*, appearance of patient about one year after operation

abnormalities of any consequence (fig. 54*a*, *b*, and *c*). His blood pressure had returned to normal and there was no question about the fact that he had neither Cushing's syndrome nor Addison's disease. The chemical composition of the blood and the daily urinary excretion of ketosteroids (10.7 mg.) were normal. Libido and potentia, which had completely disappeared, had returned. At his last examination eleven months after his second operation, his only complaint was that his physical stamina was below par as measured by his former standards. Nevertheless, he fathered a child.

Two of the remaining three patients died after a protracted illness (forty-

two and sixty-six days). Both had gross disease of the pancreas. In one there was evidence of acute and chronic hemorrhagic pancreatitis with cyst formation. This condition may have been present before her first operation if any conclusions can be drawn from the medical history. In the other patient fat necrosis was found in the tail of the pancreas. All of this is reminiscent of the "beef steak" pancreatitis that was described by Mann and Drips and at a later date by Code following adrenalectomy in dogs. Code had told me that these dogs refuse to eat and usually die but if they are fed by tube some of them recover.

In one patient at necropsy no adrenal cortical tissue could be identified. A basophilic adenoma about 2 mm. in diameter was found in the pituitary body and in the nonadenomatous portion of the gland Crooke's changes were present in approximately 40 per cent of the basophilic cells. In the case of the other patient who died traces of adrenal cortical tissue were identified. Unfortunately the pituitary body could not be examined.

The fourth patient is still alive four months after removal of most of her adrenal cortical tissue. She is slowly getting better. She no longer has any of the features of Cushing's syndrome that can be recognized on inspection. On the other hand, she does not have the appearance of patients who have Addison's disease. There is no pigmentation of the skin and repeated attempts to induce pigmentation by exposure to ultraviolet light have failed. The skin neither burned nor tanned. Comparatively early in her postoperative course she complained of severe continuous upper abdominal pain. This finally disappeared after treatment with streptomycin was instituted and at the time we suspected that she also had some type of pancreatitis. Her outstanding residual symptoms have been anorexia and profound muscular weakness. She still has mild hypertension and there is evidence of impaired renal function, although both of these seem to be improving slowly.

In all four instances it was difficult to make a distinction between those symptoms that were part and parcel of the postoperative disorder itself and those that might have been induced by treatment, either hormonal or with electrolytes. In the face of a decreased concentration of sodium in the plasma we naturally were reluctant to discontinue the administration of cortical extract and sodium chloride, and as a consequence all four patients received such treatment in liberal amounts for varying periods after operation. In one patient who had undergone partial removal of both adrenals, however, we decided to take the risk and discontinue all treatment. This was done for a period of about one month. During this month there was no appreciable change in the patient's clinical condition. The general level of the blood pressure fell but still persisted at levels that could be regarded as hypertensive. Azotemia persisted. The concentration of sodium in the blood remained low while that of potassium slowly increased and finally reached low normal values. The excretion of 17-ketosteroids in the urine remained at Addisonian levels.

At the end of this period of study testosterone propionate was administered in doses of 25 mg. three times a week. The patient's general condition immediately began to improve. Her appetite picked up, she became stronger and the waxy pallor of the skin was replaced by a faint rubor. Thus far this treatment has had no effect on the level of the blood urea

or the blood pressure. Values obtained in the last chemical analysis of the blood were as follows. sodium 135 mEq, potassium 4 mEq., chloride 104 mEq. and bicarbonate 27 mEq per liter; calcium 12.4 mg, phosphorus 3.5 mg and urea 80 mg. per 100 c.c.

From these four cases the following deductions seem to be justified

1. Most of the symptoms of Cushing's syndrome are contingent on the presence of the adrenal cortices
2. It is equally clear that in the absence of the adrenal cortices most of the symptoms of Cushing's syndrome are not contingent either on the presence of a basophilic adenoma or of Crooke's changes.
3. The persistence of Crooke's changes in one case in the absence of all demonstrable adrenal cortical tissue casts some doubt on the thesis that Crooke's changes are manifestations of a retrograde or inhibitory action of the adrenal cortices on the anterior pituitary body. However, Crooke's changes may possibly be permanent changes. Furthermore, sufficient time (sixty-six days) may not have elapsed following removal of all adrenal cortical tissue for Crooke's changes to disappear.
4. The hypertension of Cushing's syndrome does not depend entirely on the presence of the adrenal cortices. The adrenal cortices may be necessary for the original occurrence of this hypertension but they do not seem to be necessary for the continuation after it once has been initiated.
5. In cases of Cushing's syndrome removal of most of the adrenal cortical tissue may be followed by an unusual or at least atypical form of adrenal cortical insufficiency, the manifestations of which are different in many respects from those which are seen in cases of Addison's disease.
6. Subtotal adrenalectomy seems to be a hazardous procedure in cases of Cushing's syndrome. Its therapeutic utility has not been established in spite of the fact that one patient seemingly has been cured of his disorder and another is getting better.

To return to the question implied in my title, "Is Cushing's disease a primary disorder of the adrenal cortex?" My answer is, I do not know but it might well be.

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BLOOD AND CIRCULATORY ORGANS

RECENT ADVANCES IN THE TREATMENT OF CARDIOVASCULAR DISEASE*

ARLIE R. BARNES

Advances in the treatment of heart disease rarely can be referred to any one year. Rather they represent increments of knowledge accumulated over many years. While the treatment of cardiovascular disease is ever progressing, the efficacy of certain advances has been sufficiently well established to warrant mention of them in this summary. In recent years an encouraging number of successful procedures in the treatment of heart disease have been devised which constitute real advances.

CONGESTIVE HEART FAILURE

Digitalis.—It is customary to standardize preparations of digitalis in terms of cat units, a unit being defined as the dose of the drug that is lethal for cats. It is unfortunate that glycosides of digitalis are tested for potency by intravenous administration whereas oral administration is more common when they are used clinically. Gold has shown that among preparations of digitalis there is a great variation in the degree of absorption. Whereas only about 20 per cent of preparations of the digitalis leaf or of the tincture of digitalis is absorbed in the gastro-intestinal tract, practically 100 per cent of digitoxin is absorbed. It is noteworthy that only about 10 per cent of an oral dose of cedilanid is absorbed by the gastro-intestinal tract.

Since oral administration is the route of choice in giving digitalis, it is advantageous to have a drug which is absorbed completely. Digitoxin fulfills this requirement perfectly. It is feasible to administer orally a full digitalizing dose (1.2 mg.) of digitoxin with minimal prospect of gastro-intestinal irritation by virtue of the small bulk of the drug required to produce the desired effect. When given orally the quantity of cedilanid (6 to 10 mg.) or of digitalis leaf (1.2 to 1.5 gm.) required to produce a similar effect leads to nausea and vomiting before a sufficient amount of these drugs is absorbed to produce a full digitalizing effect. Except in emergencies, it is preferable to administer less than a digitalizing dose initially and to achieve full digitalization gradually by the administration of suitable additional daily doses of digitoxin. In this way one can stop short of producing uncomfortable and sometimes dangerous toxic manifestations.

From these statements it should not be inferred that satisfactory effects of digitalis cannot be obtained by a variety of standard preparations of the drug. However, since there is a variation in the percentage of their absorption by the gastro-intestinal tract, a considerable experience with a particular preparation is necessary to use it wisely.

* From the *Journal of the American Medical Association* 156:299-303 (Jan. 31) 1948.

It is seldom necessary to administer digitalis parenterally. If vomiting precludes the administration of the drug by mouth or if the situation is so grave that very prompt action is required, then it is justifiable to give a digitalis glycoside by the intravenous route. Since ouabain, when given intravenously, attains its full effect in two hours, it is the preparation of choice for quick action. An initial dose of 0.3 mg. given intravenously may be followed by intravenous injections of 0.1 mg. at intervals of two to three hours until a satisfactory effect has been obtained. It is useful to bear in mind that a dose of 3 to 5 cat units of cedilanid, digitolin or digitoxin will produce a satisfactory effect of digitalis when given intravenously, but the action of these preparations is less prompt than that produced by ouabain when similarly administered.

Mercurial Diuretics.—The congestive heart failure of many patients is not adequately controlled by treatment with digitalis. It is well understood that the administration of mercurial diuretics to such patients is indispensable. It is not so well understood that mercurial diuretics are extremely useful in keeping a patient free of edema. It must be remembered that patients can accumulate 7 to 8 pounds (3.2 to 3.6 kg.) of fluid before its presence is manifested by edema of the dependent portions of the body or by signs of pulmonary congestion. The patient may be aware of the edema because he notes the onset of dyspnea. It is useful and important to forestall the development or minimize the degree of this edema. To accomplish this, Gold advocated the daily injection of 1 to 2 c.c. of a mercurial diuretic. Since such frequent injections are burdensome to both patient and physician and since the injection often may not be needed, some more practical guide to the need for injections of mercurial diuretics should be sought. One method which I have found successful is to instruct the patient to weigh himself daily. Under standard conditions a sudden gain of 2 to 4 pounds (0.9 to 1.8 kg.) should be a signal for him to report to his physician for an injection of a mercurial diuretic. Under such a plan it has been found that the need for injections of mercurial diuretics varies from three times a week to once in two weeks or longer, and yet the patient is protected from dyspnea or the development of more than a minimal amount of latent edema.

It should be emphasized also that the rigid restriction of salt to 1.5 to 2.0 gm. daily has greatly diminished the need for the administration of mercurial diuretics in cases of congestive heart failure.

Restriction of Sodium and Allowance of Fluid.—Recently, Warren and Stead found that edema would develop in patients who had recovered from previous congestive heart failure if an excessive amount of salt was added to their diets. Under these circumstances the patients gained weight, the total volume of the blood plasma increased, the concentration of the plasma proteins decreased initially, the hematocrit determinations decreased and all of these events preceded an increase in venous pressure. Whether or not one accepts their interpretation that this failure of the kidney to excrete salt is due to the decreased output of a diseased heart and that this failure constitutes the common mechanism of heart failure, nevertheless it serves to focus attention again on the importance of sodium in the genesis of edema.

Since about the turn of the century it has been known that patients

suffering from heart disease excreted sodium poorly and that the blood sodium did not increase. From these observations it was inferred that ingested salt contributed to the edema. Renewed interest in this problem was brought about by the challenging work of Schemm who advocated a program comprised of a very large allowance of water, a sharp restriction of salt, an acid-ash diet, the use of acid-producing drugs and, occasionally, the supplemental administration of mercurial diuretics in the treatment of refractory, congestive heart failure. Further studies have indicated that restriction of salt ingested to 1.5 to 2.0 gm. daily is the most essential feature of this program and in a recent discussion White stated that some patients receiving such an allowance of salt remained free of edema even though their allowance of fluid was low. In a group of patients suffering from congestive heart failure who were kept on a greatly restricted intake of salt, Gorham and his associates studied the diuretic effect of increasing intake of fluid. They found that diuresis was enhanced by increasing the intake of fluid up to 3 liters a day, but beyond that, increasing amounts of fluid did not materially augment the diuresis. This evidence indicates that patients on a diet low in sodium do best when they are allowed to take as much water as they desire, up to 3 liters a day. It must not be forgotten that renal function in heart failure is compromised by a reduced cardiac output and sometimes by intrinsic renal disease. Under these circumstances there may still remain instances in which an intake of fluid in excess of 3,000 c.c. daily may be required to secure a satisfactory diuresis.

HYPERTENSION

Diet.—In recent years, Kempner has advocated a diet, which is known as a rice diet, in the treatment of hypertensive states which may or may not be associated with demonstrable nephritis. This diet contains no protein of animal origin and has a content of sodium of 0.15 gm. daily. Kempner observed objective improvement in about two thirds of the patients suffering from hypertension who were treated with this diet. Objective evidences of improvement included: a significant drop in blood pressure, a decrease in size of the heart, often marked improvement in important electrocardiographic abnormalities, a return to normal values of increased levels of nitrogen and cholesterol in the blood and a marked decrease in the changes in the retinal arteries, which are characteristic of hypertension.

Kempner predicted the beneficial results of this diet on the assumption that hypertension causes impairment of function of the cells of the kidneys presumably because the supply of oxygen available to these cells is decreased. As a result, the kidneys are affected by impairment of their capacity to deaminate amino acids, oxidize keto acids and form ammonia, and this failure leads to hypertension. Kempner substituted vegetable for animal proteins on the theory that the injured kidney in hypertension can no longer excrete properly the catabolic products of animal proteins. It has been calculated that 76 per cent of all the work of the kidney is spent on the excretion of urea. The concentration of urea nitrogen in the total volume of urine excreted in twenty-four hours is one fifth less in patients on a rice diet than in those on a starvation diet and, hence, the diet greatly decreases the work of the kidney.

It will be admitted by all that the rice diet is a monotonous diet. Grollman found that the restriction of sodium results in a marked decrease in blood pressure in rats in which hypertension had been induced experimentally. Believing that perhaps the marked restriction of sodium in the rice diet was the essential factor in its beneficial effect on hypertension, this investigator and his associates treated six patients who had hypertension by a more general diet containing animal proteins, but only 0.5 gm., or less, of sodium daily. In some of these cases they observed a striking decrease in blood pressure comparable to that observed when the more rigid and monotonous rice diet was used. These observers have not reported the effect of the restriction of sodium on the sodium, potassium, chloride and urea levels in the blood and urine for comparison with the results obtained by Kempner for patients who were treated with the rice diet.

These observations open up a new approach to the treatment of hypertension by dietary measures which deserve further study under carefully controlled conditions. Such studies should provide better agreement on the optimal composition of such a diet and should define its indications and limitations.

SUBACUTE BACTERIAL ENDOCARDITIS

When penicillin was first used in the treatment of subacute bacterial endocarditis, there were so many failures that many clinicians despaired of its usefulness. Further experience has shown that these failures were due, almost entirely, to insufficient doses of penicillin. The experience of Hunter permitted him to state that "the great majority of patients who have streptococcal endocarditis can be cured with sufficiently intensive administration of penicillin."

Early diagnosis is essential. The disease should be suspected in any patient with valvular heart disease who has unexplained fever for a week or more or who exhibits embolic phenomena, splenomegaly or unexplained anemia.

It is useful to establish the sensitivity of the infecting organism to penicillin in vitro, and in general the dose of penicillin given should be sufficient to maintain a concentration in the blood four or five times that required for inhibition of the infecting organism in vitro. While a dose of 400,000 to 1,000,000 units of penicillin daily will suffice in an average case, in the presence of a highly resistant strain or of relapses after treatment, doses up to 20,000,000 units daily may be required to effect a cure.

No rule can be laid down regarding the length of time treatment must be continued, for it varies with the conditions encountered in each patient. It is seldom wise to discontinue treatment in less than three weeks. Hunter advised that treatment be stopped at the end of two to three weeks. A blood culture is then made and if negative, treatment is not resumed. He found that even though such a patient continues to have fever, leukocytosis, an increased sedimentation rate and embolic phenomena, it frequently turns out that a cure results without further treatment with penicillin. Such an interruption to test the question of a cure may shorten a laborious and uncomfortable treatment that otherwise might have been prolonged unnecessarily.

It is well recognized that a patient who has valvular heart disease can acquire subacute bacterial endocarditis after the extraction of a tooth and

possibly after tonsillectomy. Such patients should always be protected by prophylactic treatment with penicillin. The administration of 100,000 units of penicillin every three hours for a day preceding and two days following such surgical procedures should suffice as a prophylactic measure.

ANTICOAGULANT THERAPY

Thrombo-embolism is a common and serious complication among patients suffering from heart failure or from acute coronary occlusion. Nay and I studied the condition of 100 patients during their immediate convalescence from acute myocardial infarction. Thrombotic or embolic complications were observed in thirty-seven cases. In four cases such complications were the cause of death, and in eight they contributed importantly to death. These complicating episodes included a second myocardial infarction (fifteen cases), pulmonary embolism (fourteen cases) and cerebrovascular accidents (eight cases).

Preliminary experience indicates that the routine administration of dicumarol to patients who have had an acute myocardial infarction, markedly diminishes the incidence of thrombo-embolic episodes and promises to reduce materially the mortality rate of this condition.

The frequency with which embolism and pulmonary infarction complicate the treatment of heart failure is too well known to deserve comment. Since it is conceded generally that these emboli arise from thrombi in the veins of the legs, one group of investigators advocates ligation of the femoral or iliac veins if nonfatal pulmonary embolism has occurred. My colleagues and I have felt that we secured equally satisfactory results by treating these patients with dicumarol. We feel that the bilateral ligation of large veins in the lower extremities is not wholly innocuous in its ultimate effects.

Pulmonary embolism occurring in medical and surgical cases ordinarily is not primarily a cardiac problem. Nevertheless, the ultimate survival of a patient who has had an attack of pulmonary embolism depends on the capacity of the heart to withstand the circulatory disturbances associated with this event. If a patient has an attack of pulmonary embolism after surgery and survives for a few hours, he has a 44 per cent chance of having a subsequent thrombo-embolic episode and an 18 per cent chance of having a subsequent fatal embolism. If treatment with heparin and dicumarol is started immediately after the episode and is administered properly, it has been shown that subsequent thrombo-embolic episodes can be prevented almost entirely. If a patient gives a history of previous thrombophlebitis or pulmonary embolism, it is feasible to preclude almost all such occurrences after surgery by starting dicumarol therapy on the third day after operation.

A successful dosage for dicumarol, as employed at the Mayo Clinic, is as follows: The dose for the first day is 300 mg. "On each subsequent day when the prothrombin is greater than 20 per cent of normal prothrombin, 200 mg. of dicumarol is given. On days when the prothrombin is less than 20 per cent of normal, no dicumarol is given. If the prothrombin drops below 10 per cent of normal during the first few days of treatment and remains there for two days, 20 to 30 mg. of menadione bisulfite is given intravenously, and thereafter only 100 mg. of dicumarol is given to that

patient on those days on which the prothrombin is greater than 20 per cent of normal."

Dicumarol cannot be administered safely unless its dosage is controlled by daily determination of the prothrombin time expressed in percentage of normal concentration of prothrombin. If serious bleeding occurs during the administration of dicumarol, a transfusion of fresh citrated blood should be given. At the same time, 60 mg. of menadione bisulfite should be given intravenously and this dose should be repeated once or twice daily until bleeding ceases.

Dicumarol is contraindicated in the presence of purpura, subacute bacterial endocarditis, renal and hepatic insufficiency or for patients who recently have had an operation on the brain and spinal cord. It should not be administered in the presence of ulcerative lesions, such as ulcerative colitis.

THE SURGICAL TREATMENT OF HEART DISEASE

Patent Ductus Arteriosus.—Patent ductus arteriosus is characterized by an absence of cyanosis, a continuous murmur over the pulmonic area and by roentgenographic evidence of enlargement of the pulmonary conus. The presence of a diastolic murmur over the pulmonic area is almost essential if the diagnosis is to be established by ordinary clinical methods. If any doubt obtains about the diastolic murmur, its presence or its absence may be established if a phonocardiogram can be obtained. A thrill is present over the point of greatest intensity of the murmur in 75 to 80 per cent of the cases. The pulse pressure is increased above the normal of 30 to 45 mm. of mercury. Since both the right and left ventricles are subject to strain and since hypertrophy of both is common, the electrocardiogram reveals no axis deviation or only slight deviation. Marked right axis deviation points to some other source of predominant right ventricular hypertrophy.

The indications for surgical closure of patent ductus arteriosus are (1) stunted growth, (2) an enlarging heart or symptoms of increasing dyspnea or both and (3) the presence of subacute bacterial endocarditis. Shapiro urged that patients who have infected ducts should undergo early operation without waiting for a possible cure of the infection by penicillin.

Opinions differ concerning surgical intervention in cases in which the diastolic pressure is normal or only slightly reduced, in which there is little or no cardiac hypertrophy and in which there are no peripheral signs of edema. However, Keys and Shapiro have estimated that the life expectancy of males is reduced by about twenty-three years and that of females by about twenty-eight years if a patent ductus arteriosus remains untreated. Since the mortality rate for surgical closure of patent ductus arteriosus is 5 per cent or less, Shapiro is of the opinion that all children should undergo this operation as soon as the diagnosis is established regardless of apparent disability or signs of disruption of the cardiac function.

Whenever possible, section of the patent ductus arteriosus rather than ligation is the most effective as well as the most practical procedure.

Coarctation of the Aorta.—The prognosis of the adult type of coarctation of the aorta has been studied by Reifstein, Levine and Gross. They found one group of cases in which the patients had attained elderly life, had only minor complaints and had had a reasonably satisfactory life.

The patients in the second group succumbed to a superimposed subacute bacterial infection. In a third group, sudden death occurred from rupture of the aorta. In a fourth group, death occurred from cardiac decompensation or from intracranial hemorrhage. In general, they found that although some individuals enjoy a long life, the prognosis usually is poor for survival beyond the ages of twenty-five to thirty years.

Gross in this country and Crafoord in Sweden have demonstrated the feasibility of the surgical treatment of coarctation of the aorta. Gross has operated on fourteen patients for this condition, with two deaths. In one a satisfactory anastomosis could not be obtained, but the patient survived the operation without any significant change in his hypertensive state. In the remaining eleven cases the results of the operation were satisfactory: normal pulsations and pressures were restored in the arteries of the legs and hypertension in the upper part of the body was relieved completely.

Gross considered that "the optimal ages for performance of this operation lie between six and twenty years." Beyond the age of twenty-five years arteriosclerosis "makes the aorta a poor vessel for manipulation and suture." It is obvious that the early identification of coarctation of the aorta offers the patient the best chance for surgical treatment, and hence for survival.

Congenital Pulmonic Stenosis.—In May, 1945, Blalock and Taussig, in an epochal report, described the first successful operation for the relief of pulmonary stenosis. They stated that the operation was indicated in cases of congenital cardiac lesions producing cyanosis when there was clinical and roentgenographic evidence of an inadequate flow of blood through the lungs. The evidence for this rests on "the absence of visible pulsations in the lung fields as observed under the fluoroscope and roentgenographic evidence that the pulmonary artery is small in size." When a patient is of sufficient age so that catheterization of the heart by the venous route is feasible, this procedure may yield information which not only confirms the diagnosis, but also is a means of determining the volume of the pulmonary blood flow. In any event, if the diagnosis is doubtful in the case of a child who has marked cyanosis, and if the prognosis for the patient is considered hopeless, Blalock and Taussig have considered that exploration is justified. When the pulmonary artery is exposed, the pressure in the artery can be measured by a water manometer attached to a needle which is inserted into the pulmonary artery. These observers considered operation inadvisable if the pressure in the pulmonary artery is more than 300 mm. of water.

Blalock and Taussig have reported that the operation is beneficial in (1) tetralogy of Fallot, (2) pulmonary atresia with or without dextro-position of the aorta and with or without defective development of the right ventricle, (3) *truncus arteriosus* with bronchial arteries and (4) a single ventricle with a rudimentary outlet chamber with which the pulmonary artery is diminutive in size.

Blalock has reported operation on 110 patients for congenital pulmonic stenosis with an over-all mortality rate of 23 per cent. In some of these cases the operation consisted of exploration and anastomosis was not performed.

The operation results in a decrease of cyanosis and clubbing of the fingers

and toes diminishes after a period. The tolerance of the children to exercise is increased greatly after operation, and some then can engage in fairly strenuous exercise.

SIGNIFICANT OBJECTIVES IN THE MANAGEMENT OF CARDIAC FAILURE IN ELDERLY PATIENTS*

HOWARD M. ODEL

Nothing is more evident than that the decays of age must terminate in death; yet there is no man, says Tully, who does not believe that he may yet live another year; and there is none who does not, upon the same principle, hope another year for his parent or his friend.

—DR. SAMUEL JOHNSON: *On the Death of a Friend*.†

In the past, medical practice has been largely concerned with diseases of youth and childhood, and problems associated with aging and the care of elderly patients have assumed a place of minor or secondary importance. However, preventive medicine, sanitation and improved pediatric and general medical practice have tended to raise dramatically the age of our population. Undoubtedly, a major factor has been the saving of younger lives by control of infectious diseases. According to United States Census figures, in 1860, 13.1 per cent of the population of the United States were forty-five years of age or older; in 1900, 17.8 per cent, and in 1940, 26.5 per cent. Conservative speculation results in the estimate that by 1980, more than 40 per cent of our population will exceed forty-five years of age, and about fifteen per cent or approximately a seventh, will be more than sixty-five years old.

EFFECT OF AGING POPULATION

These figures indicate that we have an adult population which is larger in proportion than it ever has been, and one which promises to become even greater as the years roll by. No longer can the care of aged and chronically ill patients be relegated to the background. Old age is not a disease, but the disabilities and infirmities arising from it are, and with an expanding adult population with increased longevity, the problems concerned with the practice of geriatric medicine assume compelling importance.

"CONTROLLATIVE" THERAPY

Unfortunately, many of the diseases associated with senescence are not amenable to cure. Rather, "controllative" therapy and retardation of progression must be the prime objectives. To no other group of patients do the foregoing statements apply as aptly as they do to patients suffering from cardiovascular-renal disease. In the management of such diseases in younger persons, the physician can, in most cases, successfully treat the disease and ignore the patient, whereas, when elderly patients are concerned, multiple and difficult problems may arise for two major reasons: (1) aging patients may react differently to conventional methods of therapy

* From *Geriatrics*, 2:197-204 (July-Aug.) 1947.

† Actually, his mother.

than do younger patients, and (2) in diagnosis and treatment, the entire body and mind must be considered as an integrated unit.

THREE CENTERS OF DISEASE OF AGED

In any discussion of cardiovascular-renal disease, three organs must be regarded as the major targets for attack by the disease process: the heart, the brain and the kidneys. Arteriosclerosis and its effect on vascular flow to the organ or organs in question undoubtedly heads the list of etiologic factors. However, essential hypertension, cardiac valvular defects on the basis of rheumatic endocarditis or syphilis, and chronic inflammatory lesions in the kidneys, such as *glomerulonephritis* or *pyelonephritis*, may be causative factors. Nor is any one organ singled out as the seat of attack. In fact, due to the diffuse nature of the disease process, almost invariably manifestations of involvement are found in two or more organs.

FACTORS IN DISEASE

The chief underlying factor in the incidence of myocardial insufficiency in advanced age is sclerosis of the coronary arteries. Myocardial ischemia, with varying degrees of myocardial infarction and replacement fibrosis, is the actual change. In some instances, the immediate etiologic factor is acute coronary thrombosis, whereas, in others, failure results from acute coronary insufficiency induced by any factor which throws on the damaged myocardium a load demanding more oxygen than the sclerotic coronary arteries can supply.

SYMPTOMS

With the exception of Adams-Stokes attacks and abnormal cardiac rhythms (premature beats, paroxysmal tachycardia and paroxysmal auricular fibrillation or flutter), the cardiac symptoms which most frequently bring the aging patient to the physician are manifestations of congestive heart failure. In elderly patients, these symptoms may develop suddenly, with little or no previous subjective evidence of myocardial disease. Although the usual types of heart disease tend to cause death before the age of sixty-five years, some patients who have rheumatic valvular disease or syphilitic aortitis do attain old age. Essential hypertension frequently is an associated and complicating condition which increases the load on the myocardium and adds to the impairment of cardiac function. Not uncommonly, the clinical picture is rendered worse by the coexistence of some other disease related to the aging process, such as advanced general or cerebral arteriosclerosis, pulmonary emphysema or fibrosis, impairment of renal function, diabetes mellitus or anemia. The characteristic clinical picture of congestive heart failure is well known. Left ventricular failure with cyanosis, dyspnea on effort, orthopnea and pulmonary congestion or venous engorgement, visible pulsations of the veins in the neck, tender enlargement of the liver, ascites and dependent edema associated with right ventricular failure, commonly are observed.

THERAPEUTIC OBJECTIVES

The principal objectives in the treatment of congestive heart failure in elderly patients are three: (1) measures directed primarily toward permit-

ting the heart more rest and thereby increasing its functional efficiency, (2) measures designed to relieve the consequences of insufficient cardiac function, such as peripheral edema, accumulation of fluid in serous cavities, anoxia and increased venous pressure, (3) institution of a regimen which is individualized to meet the needs of the patient and yet one which will assure, in so far as possible, maintenance of adequate circulatory function.

TREATMENT

Restoration of adequate cardiac compensation and adaptation of the patient, both mentally and physically, to the diminished state of his cardiac reserve will require considerable ingenuity on the part of the physician, for overenthusiastic therapeutic measures are likely to bring about more harm than good, and untoward effects from the administration of drugs in customary doses may be noted, such effects being due to retardation of absorption or impaired excretion.

Rest. Complete mental and physical rest is of primary importance. The amount of restriction necessary will depend on the degree of failure; it may vary from moderate or strict limitation of physical activity to absolute rest in bed for a period of weeks or months. For patients in whom dyspnea and orthopnea associated with left ventricular failure are prominent symptoms, elevation of the upper half of the body is the position of choice. The patient should not be allowed to leave the bed under any circumstances. Interruption of rest, by allowing the patient to walk to the bathroom, may be sufficient to militate against successful results from the instituted regime. Lifting the patient on a commode placed at the side of the bed, however, may be advisable for defecation, despite the indications for absolute physical rest, for should the patient tend to be constipated, it might be that attempts to use a bedpan could produce more strain than sitting on a commode. Business and family responsibilities should be strictly prohibited, and the number of visitors should be kept at a minimum. The majority of elderly patients prefer to remain at home; however, if adequate care is impossible under these circumstances, or if the patient's condition renders it necessary, hospital care may be advisable.

Sedation.—Two associated symptoms extremely difficult to contend with in patients with cardiac failure are restlessness and insomnia. Often, such patients will be rational and co-operative by day, but at night will become restless, disoriented and agitated. In the acute stage of congestive heart failure, morphine sulfate alone, administered in $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.01 to 0.016 gm.), or combined with atropine sulfate may be required at frequent intervals. Ten to 20 minims (0.61 to 1.23 c.c.) of tincture of opium, administered at intervals of four to six hours, or 50 to 100 mg. of demerol (ethyl-1-methyl-4-phenylpiperidine-1-carboxylate), may be used with beneficial sedative effect. A half to 1 grain (0.032 to 0.065 gm.) of codeine sulfate administered alone or in combination with one of the barbiturates in some cases is sufficient to control the patient's restlessness, pain or cough. In cases of mild heart failure, $1\frac{1}{2}$ grains (0.1 gm.) of phenobarbital or $1\frac{1}{2}$ grains of pentobarbital sodium (nembutal) or bromides may control restlessness and induce sleep, but caution should be exercised in administration of these agents, for many patients react poorly to them. Chloral hydrate, one of the time-honored yet least-often-used hypnotics, produces maximal benefit

with a minimal number of untoward side effects, and its use in doses of 5 to 20 grains (0.32 to 1.29 gm.) should be considered when it is desired to assure a comfortable night for the patient. If other means of sedation fail, it may be necessary to resort to the use of paraldehyde, in doses of 4 to 8 c.c. administered by mouth, or 8 to 15 c.c. administered by rectum. Frequently, when restlessness is due to episodes of paroxysmal dyspnea, either 250 c.c. of a 20 per cent solution of hypertonic solution of glucose or $3\frac{1}{2}$ to $7\frac{1}{2}$ grains (0.23 to 0.19 gm.) of aminophylline administered intravenously, or both, may quickly ameliorate the situation. The best sedative agent in a given case must be determined by trial and careful observation, and the danger of occurrence of cumulative and toxic side effects should be kept constantly in mind.

Digitalis.—Next in importance to rest in the treatment of congestive heart failure is the administration of digitalis. The maximal benefit of digitalis arises from its ability to improve the efficiency and contraction of the myocardium. For the elderly patient, the principle of administration of digitalis proposed by Withering in 1785 remains applicable, “. . . let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels; let it be stopped upon the first appearance of any one of these effects . . .” Every effort should be made to avoid gastric symptoms or other symptoms of toxicity, and the patient should be watched closely for signs of overdigitalization, such as bradycardia, premature contractions, ventricular coupling or heart block. Other symptoms of intoxication from digitalis may be blurring of vision, disturbance of distinction of color, diarrhea, oliguria and mental confusion. Elderly patients, as a rule, tolerate digitalis much more poorly than do younger persons, and may require lesser digitalizing and smaller maintenance doses. In general, one cat unit per 10 pounds (4.5 kg.) of body weight will digitalize the patient, and one cat unit taken daily is a maintenance dose.

Diuretic Agents.—Although digitalis may aid in eliminating excess stores of fluid in the lungs, liver and subcutaneous tissues through its ability to improve the efficiency of cardiac muscle and the circulation in general, diuretic agents play a role of prime importance in enhancing the elimination of edema fluid. The xanthine drugs (theophylline, aminophylline, theobromine) may be helpful not only in their capacity as vasodilators, but also for the diuretic effect they exert. Although they may be effective as diuretic agents among patients who have massive edema, their greatest usefulness perhaps lies in their action in stimulating urinary output and forestalling the recurrence of edema.

The greatest benefit in this regard comes from the use of acid salt diuretics, such as ammonium chloride and nitrate, or potassium chloride and nitrate, administered in doses of 60 to 135 grains (4 to 9 gm.) daily. Caution must be exercised in the use of these drugs in the presence of significant renal insufficiency, and if they are used under such circumstances, the possibility of acidosis, increasing renal insufficiency, or potassium intoxication due to the inability of the damaged kidney to excrete potassium normally, must be borne in mind. Furthermore, acid salt diuretics, particularly ammonium or potassium chloride, if used injudiciously, are likely to cause gastro-intestinal upsets. Yet, if renal function is entirely adequate, their use in combination with digitalis may hasten greatly the elimination

of large amounts of accumulated fluid, and their routine administration may be useful in prevention of the recurrence of edema.

Mercurial diuretics are more rapid and more powerful in their action than are either the xanthine or acid salt diuretics. Because of the hazard of consequent retention of nitrogen, or mercurial poisoning, they should not be used if the specific gravity of the urine tends to be fixed, or if the content of blood urea or nonprotein nitrogen is significantly elevated. Values for urea of 80 mg. or more per 100 c.c. of blood probably should contraindicate the use of mercurial diuretics. Albuminuria secondary to passive congestion in the kidneys is no contraindication to the use of these agents; however, when hematuria is present, caution must be observed. Rectal suppositories of salyrgan (mersalyl) or mercuzanthin, although somewhat less effective than the preparations administered intravenously, are of great advantage under certain circumstances. Recently, salyrgan and theophylline tablets and mercuzanthin tablets for oral use have been made available. The diuretic effect of these agents is less spectacular than that obtained from mercury administered parenterally, and occasional gastrointestinal disturbances are encountered when they are used. Yet, like mercury suppositories, they serve a useful purpose in certain cases, notably, among those patients with markedly decreased myocardial reserve who require frequent or persistent diuresis in addition to full digitalization in order to maintain adequate cardiac compensation. Such patients may require the periodic intravenous injection of 1 to 2 c.c. of salyrgan or mercuzanthin every seven to ten days, or one to five tablets daily taken orally, the dosage being carefully adjusted to the need of the individual patient.

Diet.—In congestive heart failure, elderly patients are especially likely to suffer from gaseous dyspepsia and constipation arising, in part, from disturbance of gastro-intestinal tone and secretion resulting from circulatory interference, and in part from edema in the wall of the gastro-intestinal tract. Sometimes, abdominal distention may cause embarrassment of the heart by means of upward displacement of the diaphragm, and occasionally nausea and vomiting create a serious problem. The diet should consist of simple, easily digestible foods, sufficient in caloric value to maintain the body weight at or slightly below the normal figure. This diet should contain adequate carbohydrate and a moderate amount of protein and fat.

It should be remembered that the vitamin reserve of aging persons invariably is lowered because of anorexia, inadequate intake of food or faulty dentition, and the diet should be fortified with vitamin supplements, particularly B and C. Restriction of sodium chloride is advisable since the water-binding tendency of the sodium ion and its effect in increasing edema are well known. In the past, during the stages of acute decompensation, it has been considered advisable to restrict the daily intake of fluid to 1,500 to 1,800 c.c. More recently, the work of Schemm, Bridges, Wheeler and White, and others has shown that fluids need not be restricted but that water should be given freely, provided that the intake of sodium is reduced to a minimum. A high fluid-low sodium regime has been found to be a useful adjunct in the treatment of certain types of refractory cardiac failure. This is particularly important in patients who have any degree of renal impairment and retention of nitrogen, for restriction of fluids in such cases only serves to intensify the degree of renal insufficiency. Constipation and strain-

ing at stool should be avoided, if possible, by the routine use of mild laxative agents, such as mineral oil, milk of magnesia in small doses, and bulk-producers such as agar or similar compounds. The use of drastic cathartic agents is to be discouraged because of their weakening effects on the patient and their tendency to provoke gastro-intestinal disturbances.

When gastro-intestinal disturbances occur, associated with nausea and vomiting, careful study is required to determine whether the symptoms are due to venous stasis, improper diet, overdigitalization, or too-heroic medication otherwise.

Other Measures.—The administration of oxygen by mask, nasal catheter or tent occupies an important place in the management of congestive heart failure, particularly in the combating of cyanosis and the relief of severe dyspnea. The cautious intravenous administration of 250 to 500 c.c. of a 20 to 25 per cent solution of glucose, once or twice daily, frequently is helpful in cases of severe congestive heart failure, because of the diuretic effect of this solution and the nutrient effect it has on the myocardium. Aminophylline (theophylline with ethylenediamine) in doses of $3\frac{1}{2}$ to $7\frac{1}{2}$ grains (0.25 to 0.40 gm.) added to the glucose may be an important therapeutic adjunct.

Venesection, one of the oldest therapeutic procedures, occupies an important place in the treatment of congestive heart failure, and its intelligent use may be a life-saving measure. Venesection is particularly effective when the pulmonary circulation has become engorged, for it reduces the volume of venous blood which makes possible more efficient cardiac contraction. Rapid removal of 500 to 600 c.c. of venous blood may be followed by definite and striking symptomatic relief, may permit the heart to keep pace or even to overcome its load, and frequently may be the turning point in restoration of function.

In some cases of very severe congestive heart failure, accumulation of free fluid in the serous cavities, pleurae, pericardium or peritoneum may be sufficiently great to interfere seriously with adequate function of vital organs, and in such cases mechanical removal of the fluid by paracentesis may be necessary. The drainage of peripheral edema by the insertion of needles or cannulas into subcutaneous tissues of extremities or genitalia, first advocated years ago by Southey, is to be discouraged.

Convalescence.—The period of rest in bed necessary in the management of an episode of heart failure depends entirely on the degree of congestive heart failure present and the response of the patient to treatment. In general, the patient should be kept in bed until all symptoms related to failure have disappeared, until an essentially normal cardiac rate and rhythm have been restored, and until all signs of abnormal accumulation of fluid in the tissues and serous cavities have cleared. However, it is advisable for the patient to start passive exercise while he is yet in bed, and he should be encouraged to start getting out of bed for short periods as soon as compensation has been restored. The periods in which the patient is allowed to be up should be gradually lengthened until he eventually is able to be out of bed for an entire day without undue fatigue, acceleration of pulse rate or dyspnea. During these latter intervals, bathroom privileges and walking about the room may be allowed, but the climbing of stairs should be delayed until the patient is stronger. As recovery progresses, activity gradually

may be increased and walking for greater distances may be permitted. Eventually, some patients who have myocardial damage of relatively mild degree may find it possible to spend several hours daily engaged in office or other light work. Eight to ten hours of rest in bed nightly are important, and the patient should be encouraged to take a rest immediately after each meal. Since an episode of cardiac failure may be ushered in with an acute infection of the upper part of the respiratory tract, prophylactic measures for the prevention of such infections should be employed. Whenever possible, it is to the advantage of such patients to spend the winter months in a warm climate, thereby avoiding the rigors of a cold winter, and at the same time reducing the risk of respiratory infections. Generally speaking, patients who have myocardial insufficiency find themselves more comfortable in low, rather than high, altitudes.

Weighing the patient at periodic intervals is important, for a sudden gain in weight frequently may be the earliest clue to retention of fluid and recurrent failure of the right side of the heart.

Psychotherapy.—Psychotherapy occupies a very important place in heart failure among elderly people. A sympathetic understanding of old age and its problems and an intimate knowledge of the individual patient's philosophy and interests in life are essential to assist in his adjustment to the diminished functional capacity of his heart on recovery from an acute episode of failure. In a definite but kindly manner, the importance of his constantly living within the limits of his decreased myocardial reserve must be impressed on him. Whenever cardiac reserve and the type of work permit, a limited number of hours of work at a lessened pace may be allowed each day or a certain number of days each week, for sudden disruption of long-established habits and motives is likely to induce mental depression and melancholy. Maintenance of an active interest in life is most essential. In the rehabilitation of patients who fail to regain sufficient myocardial reserve to carry on ordinary activity without dyspnea or precordial discomfort, occupational therapy often is helpful. The aging patient with an engrossing but not strenuous hobby is most fortunate.

SUMMARY

Enough has been written in this paper to make it evident that the management of congestive heart failure occupies a place of paramount importance in the practice of geriatric medicine, since the greatest cause of such heart failure is arteriosclerosis, a condition which is almost synonymous with aging. Because of the diffuse nature of the arteriosclerotic process, the treatment of the elderly patient must include careful evaluation and consideration of other organs, notably the brain, kidneys and digestive tract which, because of their associated functional impairment, may create problems to complicate the successful management of cardiac failure. This situation only serves to emphasize the importance of consideration of the entire body and mind as a whole in the diagnosis and management of cardiac failure in the elderly patient. For this reason, any discussion of therapy must be general, for, although the fundamentals of treatment are almost universally the same in all cases, the therapeutic details must be varied and adapted to the individual case.

CALCAREOUS AORTIC STENOSIS AND CORONARY ARTERY DISEASE*

MICHAEL J. HORAN, JR. AND ARLIE R. BABNES

This study was undertaken to determine the degree of coronary sclerosis that occurs in patients suffering from calcareous aortic stenosis. Similarly the subjective symptoms of the patients were studied to determine to what degree they might be related to the existence and degree of coronary sclerosis.

The material chosen for study consisted of the clinical histories and necropsy specimens in 100 cases of calcareous aortic stenosis selected with a view toward getting a representative number of cases in each age group. Stenosis of the aortic valve was graded according to the degree of occlusion of the aortic orifice. Less than 25 per cent occlusion was designated as grade 1; 25 to 49 per cent as grade 2, 50 to 74 per cent as grade 3 and 75 per cent or more as grade 4. The grading of the degree of sclerosis of the coronary arteries was done in the same manner as was also the grading of aortic sclerosis. In addition the hearts were studied in the gross for evidence of hypertrophy and for the presence of areas of old or recent myocardial infarction.

INCIDENCE OF SYMPTOMS AND SIGNS IN 100 CASES

Symptoms.—The most commonly occurring symptom in this series was dyspnea, which occurred in sixty-nine of the 100 cases.

The next most common symptom was angina pectoris, which occurred in twenty-eight cases. The term "angina" was applied only to those cases in which there was a definite history of retrosternal or substernal pain brought on by exertion and relieved by rest. In ten of these cases mild grades (1 and 2) of aortic stenosis were exhibited while in eighteen cases severe grades (3 and 4) of aortic stenosis were exhibited. Of these twenty-eight cases, in ten an additional complaint of postprandial abdominal distress in the form of mild pain, bloating and "indigestion" was made.

Also in five other cases in the series (not associated with angina) there was complaint of postprandial distress. In none of these fifteen cases was any associated disease of the biliary or gastro-intestinal tracts demonstrable either clinically or at necropsy.

The symptom of orthopnea was encountered in twenty-six instances. Dizziness was noted twelve times and the complaint of syncope occurred in only one patient.

Signs.—A harsh loud basal systolic murmur typical of calcareous aortic stenosis was heard in sixty patients, an atypical (usually an apical systolic) murmur was recorded in nineteen cases and in the remaining twenty-one cases no murmur was recorded on the clinical histories.

Enlargement of the heart was noted clinically in fifty-three cases. Jaundice not associated with any clinical evidence of disease of the liver or biliary tract was noted in four cases and in these, other signs of heart failure such as rales or edema were concomitant findings.

* Abridgment of paper published in full in the *American Journal of the Medical Sciences* 215 451-455 (Apr.) 1948.

Electrocardiographic tracings were made in fifty-two of the cases. As would be expected the most constant findings were those suggestive of changes in the myocardium of the left ventricle as exhibited in the fifteen cases in which frank left ventricular strain was evident and in the twelve cases in which merely left axis deviation was noted.

PATHOLOGIC CONDITIONS IN THE HEART AND BLOOD VESSELS FOUND IN ASSOCIATION WITH CALCAREOUS AORTIC STENOSIS

Degree of Aortic Stenosis Contrasted with Degree of Coronary Sclerosis.—In accord with the findings of Dry and Willis, there seemed to be a tendency for the degree of coronary sclerosis in this series to be inversely proportional to the degree of aortic stenosis. In seven cases obliteration of 25 to 75 per cent of the lumina of the ostia of the coronary arteries was noted and of these seven, angina pectoris occurred in only two cases.

Incidence of Hypertension.—Hypertension was noted in twenty-nine cases. Of these, results of funduscopic examinations were recorded in twenty-one cases; one of these examinations gave negative results, two revealed senile changes and the remaining eighteen disclosed typical hypertensive changes. In three cases in which hypertension was not detected by the sphygmomanometer, changes in the retinal arterioles characteristic of hypertension were found and in these three cases cardiac hypertrophy was noted at necropsy.

In ten of the cases of hypertension in which characteristic retinal arteriolar changes were evident and in four of the cases in which results of funduscopic examination were not recorded, angina pectoris was present.

Associated Myocardial Infarction.—Infarction of the myocardium either old or recent was found in twenty cases. In seven of these the infarction was associated with both hypertension and angina pectoris, in five with angina pectoris alone and in seven with hypertension alone. In the remaining case there was neither hypertension nor angina pectoris.

Cause of Death.—Sudden death occurred in eighteen cases. Of these, pulmonary emboli were found in six cases and one patient died apparently as the result of a reaction to plasma transfusion. The remaining eleven patients died either as a result of acute coronary insufficiency or death was in some way associated with calcareous aortic stenosis. The primary cause of death in forty-two cases was some pathologic condition of the heart; fifty-eight patients died of other causes.

COMMENT

Calcareous aortic stenosis is a disease of the aortic valve which usually becomes manifest in later life. It may be said that for all practical purposes it is a consequence of rheumatic fever. Stenosis of higher grades is almost invariably characterized by a harsh systolic murmur over the aortic area together with a coarse systolic thrill palpable anteriorly in the second and third right intercostal spaces; the diagnosis is further substantiated by the absence of the second aortic sound although this latter finding is not necessary for the diagnosis. In the lower grades or milder forms of stenosis the diagnosis may be made by demonstrating calcification of the aortic leaflets or the aortic ring on roentgenoscopic examination. The other diagnostic criteria are well known and need no further discussion.

Although in this series a positive history of rheumatic fever was elicited in only nineteen cases and a positive history of chorea was elicited in two additional cases, nevertheless the weight of evidence supports the view that calcareous aortic stenosis is rheumatic in origin.

The work of others has shown that the lesion in question is usually found in persons in the older age groups. Confirmation of this was not possible in the present series since the cases were selected with a view toward getting a representative number of cases in all age groups. However, in selecting these cases for study the impression was gained that in the great majority of all cases of calcareous aortic stenosis the lesion is first discovered when the patient is from sixty to eighty years old.

The relative mildness of calcareous aortic stenosis when compared with mitral stenosis is attested to by (1) the length of time between the actual attack of rheumatic fever and the clinical recognition of the valvular lesion and (2) by the frequency of occurrence of death from noncardiac causes (more than 50 per cent).

The angular type of pain which occurred in twenty-eight cases was fairly uniformly distributed not only with reference to the various grades of stenosis but also with reference to the various age groups. The degree of coronary sclerosis on the other hand seemed to be, in a measure, inversely proportional to the degree of aortic stenosis. In all age groups there was more or less tendency for the higher grades of aortic stenosis to accompany the lower grades of coronary sclerosis and for the lower grades of stenosis to accompany the higher grades of coronary sclerosis. No conclusion as to a cause and effect relationship between aortic stenosis and angina pectoris can be drawn from this, however, since it is known that even in the absence of an aortic lesion, necropsy studies in a case in which the patient exhibited a severe anginal syndrome during life may, in rare instances, reveal only minimal coronary sclerosis. Conversely patients who never complained of angina may have coronary sclerosis, grade 4, which is observed at necropsy.

Hypertension may occur in calcareous aortic stenosis with the same frequency as it does in other organic heart diseases. In this series the incidence of hypertension was 29 per cent; eight of these patients had grade 1 stenosis of the aortic valve, nine grade 2, eight grade 3, and four grade 4. From funduscopic studies in this series there is no reason to believe that the hypertension associated with calcareous aortic stenosis differs in any way from ordinary essential hypertension since eighteen of the twenty-one pairs of fundi which were studied showed changes typical of essential hypertension. No retinal vessels in the series exceeded a grade 2 narrowing or a grade 2 sclerosis. White and Jones in 1928, in a study of 3,000 patients with cardiac symptoms, 2,421 of whom had organic heart disease, found the incidence of hypertension to be 29.2 per cent among those with organic disease.

The fact that ten cases of angina pectoris occurred in association with the less severe grades of coronary sclerosis (but more severe grades of aortic stenosis) and that eighteen cases of angina occurred in association with the more severe grades of coronary sclerosis (but less severe grades of aortic stenosis) suggests that the degree of coronary sclerosis does not explain all the mechanisms operating in the anginal syndrome. Other factors to be taken into consideration are (1) the complete clinical picture which includes

such points as age, pain threshold of the patient, presence or absence of an associated disease such as diabetes, hypertension and so forth, and the presence or absence of a valvular cardiac lesion particularly of the aortic valve and (2) the complete pathologic picture which not only includes a study of the coronary arteries and their ostia but also the degree of scarring and hypertrophy of the myocardium and the degree of dilatation of the cardiac chambers.

EXPERIENCE WITH ANTICOAGULANTS IN THE MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION*

ROBERT L. PARKER

Dicumarol alone or dicumarol in combination with heparin has been used in the management of fifty patients with acute myocardial infarction. The mortality rate in this series was 10 per cent. There were only two instances of secondary thrombo-embolic complications in this series (4 per cent), in contrast to an incidence of 37 per cent for such complications in a control series (Nay and Barnes) of 100 patients whose treatment was, in all respects, similar except that anticoagulants were not used. No serious complication occurred as the result of the use of anticoagulants and the results to date seem most favorable. I believe the results warrant a continuation of the use of these anticoagulants in acute myocardial infarction.

CHRONIC CONSTRICTIVE PERICARDITIS: RESULTS OF PARTIAL PERICARDIECTOMY AND EPICARDIOLYSIS IN THIRTY-FOUR CASES†

STUART W. HARRINGTON

The surgical treatment of cardiac lesions has developed more slowly than other fields of surgery because of the difficult problems which these lesions present and the hazard associated with their operative treatment. The problems in this field of surgery are concerned not only with technical surgical consideration but also with the diagnostic difficulties encountered, and it is only because of the close co-operation of the clinician and the surgeon that progress in this field has been made possible.

One of the important advances in the surgical treatment of cardiac lesions in recent years has been made in the treatment of cardiac tamponade associated with chronic constrictive pericarditis. Galen and Morgagni recognized the condition at necropsy but Lower is given the credit for the first

* Abstract of paper published in full in the *Journal of the Iowa State Medical Society*, 37: 481-486 (Nov.) 1947.

† From *Modern Concepts of Cardiovascular Disease*, Vol. 16, (May) 1947, 2 pp.

clinical description of the disease in 1669. In 1895, Weill suggested that the condition would come within the province of surgery by delivering the heart from the shell which strangles it. He stated that after the adhesions reach a fibrous stage they act independently of their original cause and that medical therapy is illusory. D  lorme, in 1898, proposed an operation for separation of the adhesions between the heart and the pericardium either by sharp or blunt dissection. Although he made many pleas for this type of operation before the clinical societies of Paris, this procedure was not carried out until 1913 when Rehn followed D  lorme's proposal and operated on four patients with constrictive pericarditis. Two of the patients died at the operation and the remaining two died within the next two years. Rehn not only followed D  lorme's suggestion of separating the adhesions but also resected a portion of the pericardium. Sauerbruch, who worked independently in the same year, reported a case in which partial pericardiectomy was successful. Braner in 1902 suggested removal of the precordial bony structures so that the tug of the heart would be on the soft yielding structures of the thoracic wall. This procedure is only effectual in cases in which the adhesions involve the pericardium and thoracic wall and the pericardium is not adherent to the heart muscle, it offers little if any benefit for true constricting pericardium which compresses the heart muscle. When this condition exists, the actual removal of the constricting scar from the heart muscle is the only effectual procedure.

The work of these pioneers in establishing the fact that constrictive pericarditis was amenable to surgical treatment has stimulated clinical studies and investigative work in this field.

Schwieden, of Germany, and Beck, Churchill and Blalock in the United States, have done a great deal of work on this condition and have had considerable experience with its surgical treatment.

Many different terms have been used to designate cardiac tamponade, such as "adhesive pericarditis," "Pick's syndrome" and "chronic constrictive pericarditis"; however, the last term is the one most generally accepted to designate an inflammatory lesion of the pericardium and epicardium in which fibrous adhesions often associated with deposits of calcium and occasionally pockets of encapsulated fluid form between these coverings of the heart and in which the inflammatory scar contracts around and onto the heart muscle to such a degree that it interferes with the normal diastolic and systolic functions of the heart and causes impairment of circulation. This condition is of unusual interest because its cause is often obscure, its occurrence is infrequent, its clinical course is slow and it causes progressive disability.

The circulatory failure produced by this condition develops slowly and insidiously. It is due primarily to progressive mechanical interference with the action of the heart and not to intrinsic cardiac disease except in those cases in which it has been present for a long time and some degree of associated myocardial atrophy has resulted from the constriction. The primary cardiac fault in this condition is physiologic, owing to the fact that the dense inflammatory scar encasing the heart muscle prevents the heart from attaining its normal diastolic volume and thereby causes increased tension in the chamber of the right side of the heart which results in an inflow stasis.

The diastolic filling of the heart is less than normal, which results in decreased ventricular output of blood. It is probable that other factors contribute to the decreased ventricular output to a lesser but significant degree. One of these factors is interference with systolic contraction of the ventricles due not only to fixation of the scar to the myocardium but also to myocardial atrophy and degeneration from limited action as well as from the original infectious process.

The primary infectious process which causes constrictive pericarditis may not be and often is not associated with acute symptoms which indicate that the pericardium has been involved.

The cause is of considerable interest and importance and there is some difference of opinion concerning the type of infecting organism. Every effort was made to determine the causative agent in a series of thirty-four cases in which I operated. This study definitely proved that the etiologic agent was tuberculosis in five, or 15 per cent, of the cases. This type of infection, therefore, should always be considered as a possible cause of the disease. In twenty-nine, or 85 per cent, of the cases, the type of primary infection was unknown.

It has been stated by some authors that rheumatic fever is one of the chief causes of this disease but it is of interest to note that in only one of the cases was there a previous history of rheumatic fever and in this case the microscopic study of the tissue removed at operation revealed that tuberculosis was the etiologic agent. I do not believe it possible or advisable to attempt to draw any definite conclusions as to the cause of the disease from this relatively small group of cases.

The two most common conditions with which constrictive pericarditis is most likely to be confused clinically are cirrhosis of the liver and congestive heart failure due to intrinsic cardiac disease. In most instances, however, the sequence and insidious onset of symptoms, when they are correlated with the physical and laboratory findings, are sufficiently characteristic to make a definite diagnosis of constrictive pericarditis.

The most important clinical and laboratory findings in the thirty-four cases were increased venous pressure, prolonged circulation time, enlargement of the liver with impaired function, ascites, faint heart sounds and diminished pulsations, infrequency of cardiac murmurs and low blood pressure and pulse pressure. The heart usually was of normal size or slightly enlarged but was not dilated.

The number and severity of subjective symptoms increase progressively with the course of the disease. The effects of the disease cause increasing disability which gradually becomes complete unless relieved by surgical treatment.

SURGICAL TREATMENT

Patients who have been selected for surgical treatment require preoperative preparation. Measures to reduce the ascites and the peripheral edema and to improve the function of the liver comprise the chief objectives in preoperative treatment.

I prefer general anesthesia produced with cyclopropane in combination with some ether, administered under positive pressure by the use of an intratracheal tube. In my earlier cases I used cyclopropane only. The

reason for combining it with ether is to lessen the occurrence of cardiac arrhythmia, which may occasionally be associated with cyclopropane anesthesia.

During the operative procedure it is important not to open the pleural cavity, particularly at an early stage of the operation, because of the respiratory difficulty that often follows. I defer the wide separation of the left pleural attachments to the outer wall of the pericardium until after the pericardial scar has been fully separated from the myocardium.

The most important part of the operative procedure is the release of the myocardium from the constricting scar. I have suggested the term "epicardiolysis" to designate the separation of the scar of the innermost layer of the pericardium from the myocardium. This procedure is very important; it is done in addition to the resection of a portion of the pericardium and epicardium and extends over a much larger area of the heart muscle than the area from which the pericardial scar is resected.

Opinions differ concerning the amount of pericardial scar that it is necessary to remove as well as concerning the amount of scar to be separated from the heart muscle. I believe it is advisable to separate the scar from the ventricles and as much as possible from the right auricle and orifice of the inferior vena cava. It is of particular importance to sever the attachments of the right ventricle to the diaphragm. It is of equal importance to separate the apex of the heart from its attachments and I believe that this should be done early in the operation, if possible. Separation of the heart muscle from its fixed attachments to the diaphragm is one of the most important considerations in re-establishing the action of the heart. Improvement in the function of the heart often is noted immediately after adhesions of the apex and right ventricle to the diaphragm have been severed.

After the scar has been separated from the heart muscle, the amount of pericardium to be resected depends on the character of the scar and to some extent on the fixation of the pleural attachments to the outer wall of the pericardium. I believe it is advisable to resect as much of the anterolateral wall of the pericardium as possible without injuring the pleura. By careful dissection, the pleural attachment to the pericardium can be separated to approximately the position of the left phrenic nerve, and the entire anterior portion of the thickened pericardium extending beneath the sternum is resected. In cases in which attachment of the pleura extends high on the pericardium, as it often does when calcium is present, it may be impossible to resect an adequate amount of pericardium without injuring the pleura. In these cases, linear incisions into the remaining cut edges of the pericardial scar will produce a much wider opening of the pericardium.

The importance of separating and removing sufficient scar to release the heart cannot be overestimated because, if a sufficient amount is not separated and removed, cardiac action will continue to be impaired. This not only will eliminate the possibility of ultimate recovery from the disease but will interfere with the immediate recovery from the operation.

RESULTS

The rapidity and completeness with which recovery occurs after operation depend on several factors, the most important of which are the amount of myocardial atrophy and degeneration, the amount of hepatic damage

and the thoroughness with which the constricting scar has been removed from the impaired heart. Improvement may be noticed soon after the operation but it often proceeds slowly and progressively. Complete recovery may not occur for many months. This is somewhat dependent on the duration of the disease before operation.

Of the thirty-four patients operated on, twenty-seven recovered from the operation and seven died in the hospital after operation; the operative mortality, therefore, was 21 per cent. Although this mortality is relatively high, it is commensurate with the seriousness of the disease and with the fact that the mortality rate ultimately would have been 100 per cent without surgical intervention.

Eighteen of these thirty-four patients can be considered cured at this time and two patients, who have been operated recently, six and three months ago respectively, have shown marked progressive improvement. Of the remaining seven patients who recovered from operation, three have shown a moderate degree of improvement but it is not likely that they will ever be considered cured. Four patients have died since the operation. The deaths of three of these four patients were due to continuation of the disease, two of the three deaths were due to progressive cardiac failure two years and one month, and seven years and six months, respectively, after operation, and one was due to tuberculous peritonitis two years and three months after operation. In the remaining case, the patient was improving satisfactorily from operation but unfortunately died of pneumonia seven months after the operation.

I believe that the percentage of deaths can be decreased by earlier recognition of the disease, which would permit earlier institution of surgical treatment.

Patients who respond to operative treatment for chronic constrictive pericarditis obtain one of the most dramatic results produced by operation and it is most gratifying to see these patients, who otherwise would be doomed to a slow lingering death, restored to health and usefulness.

ACUTE NONSPECIFIC PERICARDITIS*

HOWARD B. BURCHELL

The interest of clinicians in acute pericarditis among adult persons has been stimulated during the past ten years with the recognition of the characteristic electrocardiographic pattern and of the symptom complex in which pain may be the predominant feature. Although pericarditis has been recognized as a complication of pneumonia and septicemia or part of the clinical picture of rheumatic fever, tuberculosis, disseminated lupus erythematosus, myocardial infarction and uremia, there is a group of pericarditic patients in whom the etiologic factors are unknown or obscure.

This group of patients, who have a condition of undetermined etiology,

* From *Modern Concepts of Cardiovascular Disease*, Vol. 16, (Mar.) 1947, 2 pp.

is considered to be important because the clinical features are related mainly to the pericarditic inflammatory process, and the severe pain may simulate that arising from acute myocardial infarction. The terminology best suited to this clinical syndrome is difficult to choose because of the *undoubted variability in the causative agent and because the pericarditis probably is always secondary, even though it assumes a primary role in initiating the patient's complaints*. Diagnostic phrases such as "acute non-suppurative," "acute serofibrinous," "acute idiopathic," "primary idiopathic," "acute benign," and "acute nonspecific" pericarditis, have been used. The last term is the one that is preferred herein. It has been frequently customary to modify the diagnostic term by a phrase which indicates that the disease has a high incidence among young adult persons. Recent observations, however, have emphasized that the condition may occur in any decade of adult life, and that it is not limited to the younger age group. In a few patients who have had an attack of this type of pericarditis, recurrences of a similar benign type of pericarditis have been experienced, and for this syndrome the term "acute relapsing pericarditis" may be suggested.

CLINICAL FEATURES

The patient usually dates the beginning of his illness to the onset of the thoracic pain, and the infection in the upper part of the respiratory tract which frequently precedes the condition may have been forgotten. The pain may begin with dramatic suddenness, with immediate incapacitation of the patient, or it may be mild and intermittent for several days before its greatest severity is attained. In rare instances after the onset of severe pain, there may be circulatory collapse and the patient may be observed to be in a state of clinical shock. The distribution of the pain may be widespread over the whole thorax, or localized in the substernal, precordial, epigastric or interscapular region. Shoulder tip pain may occur, and pain may extend into the arms. The pain may be described as "aching" or "squeezing," and is characteristically aggravated by breathing, coughing, twisting of the trunk and sometimes by swallowing. The patient may feel most comfortable in the sitting position. The pain in its severe form rarely lasts for more than a few hours and gradually becomes moderate over a period of two or three days. Some pain may persist in a mild form for many weeks, long after otherwise complete recovery.

Marked differences occur in the severity of the illness. In not a few cases, with the disappearance of pain in two or three days, the patient feels exceptionally well and convalescence is a matter of only a week or two. In the majority of cases, however, general malaise, fatigability and vague pains in the thorax persist for some weeks. In a few other patients, the fever may persist for two to three weeks and the ambulatory regime may be delayed, but convalescence may then be as rapid as in cases in which fever is of short duration.

In regard to the physical signs, the pericardial friction rub is by far the most important of these. If the patient has been under observation continuously throughout all phases of his illness, it is probable that this diagnostic sign will always be heard. Three patients have been seen who spontaneously gave the information that at the onset of their illness they were conscious of a friction rub within their thorax, correlated with the heart

beat. The fever, which is usually maximal on the first day, rarely exceeds that indicated by a temperature of 102° F. (38.9° C.) and the accompanying tachycardia is slight or moderate. In one instance a clinical picture developed which suggested cardiac compression. The patient, a young soldier admitted to an overseas hospital with thoracic pain and in a state of shock, showed an increase of venous pressure in the midphase of illness. Pericardiocentesis was carried out. The removal of a small amount of fluid had little effect on the clinical condition, but eventually convalescence was rapid and recovery complete.

LABORATORY FEATURES

The laboratory observations in cases of acute nonspecific pericarditis reveal mild leukocytosis and an increased sedimentation rate, the former returning to normal within the first week and the latter within two weeks, as a rule.

Roentgenograms of the thorax made during the course of the acute pericarditic illness may be of great value because of changes in the size of the cardiac shadow. There can be no doubt that the cardiac silhouette may increase greatly in size when it is compared in teleroentgenograms, and this enlargement may appear as early as twelve hours after the onset of the pain. A certain degree of skepticism may be encountered in regard to the thesis that the increase in size represents actual cardiac dilatation and not pericardial effusion. Such a thesis, however, is accepted by many who have intensively studied the problem. In a few instances, the roentgenogram of the thorax made in the early phase of the illness will reveal mild pneumonitis, usually basal in distribution.

The electrocardiographic pattern has been described in detail by many authors and referred to by Barnes and me. The essential components of the diagnostic pattern are the elevation of the RS-T segment with a dome-shaped or peaked T wave in the early stage, and negativity of the T waves in the late phase. There is no depression of the RS-T segment at any time; the T waves never show a classic reciprocal relationship in leads I and III, and no Q pattern ever develops in the standard or chest leads.

DIFFERENTIAL DIAGNOSIS

When the diagnosis of acute pericarditis seems evident, the search for an etiologic factor should not be abandoned too quickly. Rheumatic fever and tuberculosis are two conditions that always have to be considered, but pericarditis due to these causes is more often painless and has a different clinical course.

As a general rule, the diagnostic problem will be in the distinction between the pain of pericarditis and that of acute myocardial ischemia or infarction. One of the main points in differential diagnosis is the aggravation of the pericarditic pain by breathing or body movements. Although the pain of pericarditis may extend into the neck and both shoulders, it usually will not spread down into the elbow and wrist joints. The presence of fever, a pericardial rub and an increased sedimentation rate on the first day of the pain, instead of after a period of some days, may be helpful in support of the diagnosis of pericarditis. The other conditions that may be considered in differential diagnosis are lesions in the posterior part of the mediastinum.

such as mediastinitis, pneumomediastinum, diaphragmatic hernia, or aortic dissection. If the possibility of the presence of such conditions is kept in mind, they should not give trouble in differential diagnosis.

PROGNOSIS

In spite of the fact that the pathologic processes may vary in different patients, the prognosis seems to be universally good. The condition of the fourteen patients reported on by Barnes and me has been closely followed, and nothing has been learned to change the opinion that acute pericarditis in adult persons usually is a benign type of disease without sequelae. There is now an additional group of twenty-nine patients whose condition has been diagnosed, since that time, by the cardiac consultants at the Mayo Clinic, as acute nonspecific pericarditis with pain, and the condition of these patients has been followed for periods of one year to five years. Further emphasis may be placed again on the recurrent vague precordial pains which may persist for weeks, long after the convalescence is otherwise complete. In such patients with persisting pains, particularly if the pains are associated with a prolonged asthenic state, functional symptoms may make their appearance and tax the physician's patience and skill in maintaining the patient's morale. At least four patients have had recurring attacks, with the electrocardiogram returning to normal or nearly so between the attacks. One patient, a physician (case 5, Barnes and my series), was, at the time of the present writing, enjoying a very active life and carrying on a busy consulting practice in spite of three recurrences.

COMMENT

Many aspects of the benign syndrome of acute pericarditis in adult persons lack adequate explanation. Among the problems presented are the etiologic agents responsible for the illness, the involved tissue within the thorax from which the pain stimulus originates, the factors responsible for the circulatory collapse that may occur with the onset of pain, the mechanism of cardiac dilatation, the reasons for the persistence of the pain and the nature of the electrophysiologic disturbance which gives rise to the electrocardiographic picture.

Eventually, it may be possible to reach a more clear-cut opinion as to the causes of the nonspecific pericardial inflammation, but at present it is assumed that the serous surfaces of the pericardium may respond similarly to a number of directly infectious agents or products of such agents. The high incidence of pericarditis of unknown etiology among adult persons has been noted by Nay and Boyer and Smalley and Ruddock.

The nature of the distribution of pain and the aggravation of the pain by breathing, swallowing and movements of the trunk suggest that the pain stimulus arises in the parietal pericardium and that it is more truly pleuro-pericardial than pericardial in origin. This concept is not only in conformance with the results of Capps's observations on pericardial pain, but it explains why pericarditis, within the pericardium, may be painless. The severe circulatory collapse that may occur is associated with severe pain, and it might more readily be believed that the mechanism is analogous to the state of severe shock that may be observed in some cases of "chokes"

in decompression sickness, and to spontaneous pneumomediastinum, than to some direct effect on the myocardium.

The mechanism of the cardiac dilatation is obscure, in spite of analyses of the possible causative factors. The possibilities of severe myocarditis, coronary insufficiency caused by arterial spasm, superficial myocardial edema limiting systole and the loss of the constraining influence of the pericardium, are imaginative factors, without basis in real evidence. It would be easier to assume pericardial effusion as a basis for the enlargement of the cardiac silhouette, but roentgenographically and clinically the evidence is against the diagnosis of pericardial effusion.

Acute pericarditis constitutes one of the best examples of how marked electrocardiographic changes may exist in the presence of relatively normal cardiac function and structure. The correlation between the electrocardiographic changes and subepicardial myocarditis has been emphasized, but actually such emphasis may mislead one into thinking too rigidly of structural changes rather than, biochemically, of cellular and membrane function. In other words, it is believed that surface injury might occur without much histologic aberration, and that the ingress of inflammatory cells in an area would not necessarily mean change in cellular depolarization and repolarization. The extent of segment elevation in the chest leads, and the position on the chest at which the maximal change occurs, are unpredictable. Two possible explanations for variation in the chest-lead patterns are, first, one's ignorance of the uniformity of the epicardial injury, and second, the fact that in some positions on the chest, anterior and posterior injury potentials may partly neutralize one another.

The points having been made that the pain is related to the exterior of the pericardium and the electrocardiographic changes to the epicardium, it might be expected that the two conditions would not necessarily parallel one another. Indeed, as is well known, marked electrocardiographic changes characteristic of pericarditis may exist without pain, and it should be expected occasionally that thoracic pain characteristic of pericarditis will be encountered without the electrocardiographic pattern of pericarditis. After the results of experimental work, there was some hope that it would be possible to localize pericarditis in some instances, and to correlate the electrocardiographic pattern with the distribution of pain. To date, there has been no case in which the diagnosis of localized pericarditis has been made, and there has been no correlation of the electrocardiographic pattern with the distribution of pain recognized.

SUMMARY

The salient points in the problems of the diagnosis of acute pericarditis have been reviewed. Emphasis has been directed toward the clinical syndrome of severe pain and the electrocardiographic abnormalities.

THE EFFECT OF SYNTHETIC LACTOBACILLUS CASEI FACTOR ON THE BLOOD CHANGES INDUCED BY GASTRECTOMY IN THE RAT*

GEORGE M. HIGGINS, DWIGHT J. INGLE AND OLIVER R. JONESON

A study is reported of the effects, on the blood changes induced by gastrectomy in white rats, of giving synthetic *L. casei* factor. Sixteen adult male rats were gastrectomized. Of these, six survived for five months and were used as test animals. All were without obvious signs of any gross pathologic changes, as a result of the surgical intervention, but all showed evidence of malnutrition, manifested by progressive loss of weight, and by their rough and discolored coats. *Light nongastrectomized rats served as controls.*

Five months after gastrectomy, the total erythrocyte counts were normal, the hemoglobin levels were reduced and marked microcytosis had developed. Seventy-two hours after a single administration of synthetic *L. casei* factor (200 micrograms), a slight but significant elevation of the percentage of reticulocytes was obtained, but there were no changes in the total erythrocyte counts, the volumes of erythrocytes, the hemoglobin levels, or the total leukocyte counts.

When *L. casei* factor was added to the purified diet, at a level of 100 micrograms per gram, and fed to gastrectomized rats for fourteen days, changes did not occur in the total numbers of erythrocytes, the volumes of erythrocytes, or the levels of hemoglobin. Slightly significant increases occurred in the percentages of reticulocytes and markedly significant increases occurred in the total numbers of leukocytes. This increase of the number of leukocytes was due entirely to a myeloid stimulation, for the numbers of lymphocytes remained unchanged. There was a marked increase of the total number of circulating myelocytes, metamyelocytes, and mature neutrophilic granulocytes.

When *L. casei* factor was injected intraperitoneally daily for fourteen days in amounts equivalent to 400 micrograms, a marked myeloid stimulation likewise occurred. Of the total leukocytes present, 22.6 per cent were myelocytes, 7.0 per cent were metamyelocytes, and 46.6 per cent were mature neutrophilic granulocytes. Thus of the total number of circulating leukocytes, 76.2 per cent were neutrophilic granulocytes. The parenteral administration of the factor was more effective than providing the factor in the diet.

* Abstract of paper published in full in the *Journal of Laboratory and Clinical Medicine* 32 653-643 (June) 1947.

THE STRESS AND THE ELECTROCARDIOGRAM IN THE INDUCED HYPOXEMIA TEST FOR CORONARY INSUFFICIENCY*

HOWARD B. BURCHELL, RAYMOND D. FRUITT AND ARLIE H. BARNES

The induced hypoxemia test has been established as a procedure which plays a small but useful role in the diagnosis of coronary sclerosis. Proper emphasis has been placed upon the potential dangers of the test. However, if the patients to be subjected to the procedure are properly selected and if precautions in administration of the test are observed, the danger entailed is minimal and does not contraindicate use of the test as a diagnostic adjunct. In the 730 tests carried out at the Mayo Clinic for the diagnosis of coronary sclerosis, no fatalities have occurred. In the majority of the patients who have had an alarming reaction, it is now believed that the patient's age or his affliction by complicating illnesses were etiologic factors. The factor of danger, however, does limit application of the procedure in many investigations of clinical and electrocardiographic problems of coronary insufficiency, in which otherwise it would be most valuable.

TABULATION

DATA ON 288 PATIENTS THREE TO SIX YEARS AFTER A SATISFACTORY INDUCED HYPOXEMIA TEST FOR THE DIAGNOSIS OF CORONARY SCLEROSIS

Clinical diagnosis and result of hypoxemia test	Patients		Condition			Not traced
	Total	Traced	Same or improved	Worse	Patients dead	
Angina pectoris, positive test	86	57	30	11	16	29
Angina pectoris, negative test	43	33	17	10	6	12
Possible anginal syndrome, negative test	56	39	26	6	7	17
Noncardiac thoracic distress, negative test	101	63	57	5	1	38
Total	288	192	130	32	30	96

An attempt was made to obtain information on the patients who had been given the hypoxemia test for coronary insufficiency during the first three years it was used, allowing follow-up periods of three to six years. Questionnaires were sent to 300 patients and reports were obtained concerning 204. Of these 204 patients traced, twelve were not considered further because they had had an unsatisfactory hypoxemia test; thirty were dead and there was presumptive or definite evidence that each death was related to coronary insufficiency (tabulation).

* Abstract of paper published in full in the *American Heart Journal* (In press)

The average age of the group of thirty patients who died was forty-seven years, with a range from thirty-five to sixty years. The average duration of life after the test in this group was eighteen months, with a range from three days to forty-four months.

Of this group of thirty patients, nine had normal control tracings and a pain response; of these nine, seven had positive and two had equivocal results in the electrocardiographic study. Of twelve patients with normal control electrocardiograms and marked diagnostic electrocardiographic changes with hypoxemia, seven had pain. The data might be interpreted as indicating that pain due to true coronary insufficiency is practically always associated with some electrocardiographic changes of the ischemic type but that such electrocardiographic changes frequently occur in hypoxemia without anginal pain.

The experience gained from the performance of approximately 730 induced hypoxemia tests for the diagnosis of coronary sclerosis after the method of Levy has reaffirmed our previous views as to the clinical value of the test. In selected cases the test has been of great assistance in the diagnosis of coronary insufficiency, and when coronary sclerosis of clinical magnitude is present, one may expect a positive result in about 50 per cent of cases. There has been an understandable tendency sometimes to employ the procedure as an exclusion test; one must constantly be on guard to avoid such an error. Among the patients that have been studied are a large number of physicians, young patients with essential hyperlipemia and patients with diaphragmatic hernias. In the last group of cases, the test has not infrequently supported the clinical impression that symptoms were related to coronary insufficiency and not directly to the hernia. So far it has been impossible to ascertain the degree of coronary disease that must be present before a positive reaction to the test is obtained, but it is known that severe sclerosis may be present with a negative reaction.

The continuous study of the arterial saturation throughout the test has added to our knowledge of the physiologic stress imposed but otherwise it has been of only slight help in the interpretation of the results. Positive results have been obtained both with the low and the fairly high arterial hemoglobin saturations. One gains some knowledge of the ventilatory function during the test so that one can caution the patient against excessive ventilation. When saturation values have fallen to less than 75 per cent, and particularly to 70 per cent, our attention to the patient's condition has been further alerted and such a low saturation has not been allowed to continue for more than a few minutes. For the routine test, the incorporation of the oximeter is not necessary, although the only disadvantage to the use of the oximeter has been the longer control period that is required to permit proper equilibration of the instrument.

One may emphasize again the precautions which must be observed in order that the test may be called a safe clinical procedure. First, in the selection of the patients the following persons should be excluded: those who are more than sixty years old, those with obviously enlarged hearts, those with previous myocardial infarction, those with pulmonary disease, such as emphysema, and those who are generally ill. Secondly, the physician who has some familiarity with the patient's symptoms should personally supervise the test. The knowledge that death from anoxia can occur at

relatively low altitudes has not caused decrease in one's respect for the severity of the stress imposed by the hypoxemia test. However, the short time the patient is exposed to low oxygen tensions undoubtedly constitutes an important safety factor.

Our opinion as to the increased stress imposed upon the subject when the test is performed in localities at higher altitudes than that of Rochester has not changed since our first report. The stress is increased, but partial protection is present through the normal acclimatization to altitude. It is believed that the choice of a 10 per cent oxygen mixture was a fortunate one, and at this time we would doubt the wisdom of using a lower percentage.

Our studies with special electrocardiographic leads, namely, the unipolar extremity leads which have been routinely used in the test for eighteen months, have elucidated the genesis of the electrocardiographic pattern but have not contributed significantly to the evaluation of a positive or negative electrocardiographic test. Our electrocardiographic interpretations support the theory that a gradient of injury, increasing toward the endocardium, exists, which is consistent with the theory of injury discussed by Johnston and Wilson. As the interpretation of the test is based on the quantitation of the electrocardiographic changes, it is expedient to use leads where these changes are summated. For this reason the CR leads have certain advantages in the routine tests.

AN EVALUATION OF THE ESOPHAGEAL ELECTROCARDIOGRAM IN THE DIAGNOSIS OF HEALED POSTERIOR MYOCARDIAL INFARCTION*

HOWARD B. BURCHELL

Esophageal electrocardiograms are easily obtained, and the use of small but heavy electrodes with thin flexible lead wires, together with a direct writing electrocardiographic machine, has facilitated the recording of them. A study of the value of such electrocardiograms in the diagnosis of posterior myocardial scars (previous infarctions) has been carried out in a series of fifty cases. The fifty cases comprised (1) persons with known previous infarction with and without diagnostic electrocardiographic sequelae, (2) persons with lengthened Q waves in lead III with and without angina pectoris, (3) a few persons with right bundle-branch block with suspected infarction and (4) several patients having anginal pain with the "electrocardiographically vertical" variant of the left ventricular strain pattern. The esophageal electrocardiogram at the ventricular level has shown great variability. In about 10 per cent of cases it retains the form characteristically seen at esophageal levels. When such a form is not present, the electrocardiogram usually simulates the configuration of the left leg unipolar lead, in both "electrocardiographically vertical" hearts and "transverse" hearts. The latter lead (V_F or aV_F) usually is of greater help in the evalua-

* Abstract, read at the meeting of the American Federation for Clinical Research, Chicago, Illinois, October 30, 1947.

tion of the significance of prolonged Q waves in derivation III than are esophageal leads. The changes in the esophageal lead that have been most distinctive when myocardial infarction has occurred have been widening and splintering of the initial downward wave and a splintered downward deflection not followed by an R wave. In only one case has a Q wave followed by elevated RT segment been observed. The T wave direction appears to vary independently, and has given no help in diagnosis. It appears that an esophageal electrode often continues to be influenced by cavity potential, even when the auricular complex shows no intrinsic type deflection, hence, the records obtained usually are not the immediate counterparts of a direct lead from the diaphragmatic area of the ventricle. With the use of the electrodes described, extracardiac potentials produce marked aberrations in the tracings in only a few patients.

THE PRINCIPAL CLINICAL FEATURES OF PATENT DUCTUS ARTERIOSUS AND THE TETRALOGY OF FALLOT*

ROBERT L. PARKER

Owing to the rapid progress which has been made in the past few years in the surgical treatment of certain types of congenital cardiac malformations a new interest has developed in the entire field of congenital heart disease. No longer is the accurate diagnosis of congenital cardiac malformations of academic interest only. It now becomes the responsibility of the physician to attempt to make an anatomic diagnosis in each case in order that individuals suffering from these defects may not be denied surgical treatment when it is indicated. With modern diagnostic aids, an understanding of the embryologic development, a knowledge of the altered circulatory dynamics encountered and an acquaintance with the clinical picture, which is often quite characteristic, an accurate diagnosis is usually possible in most cases of congenital cardiac deformities. At the present time surgical treatment has been successfully carried out in patent ductus arteriosus, in coarctation of the aorta and in pulmonary stenosis usually associated with the tetralogy of Fallot. In this presentation I should like to point out the principal clinical features encountered in two of these conditions; namely, patent ductus arteriosus and the tetralogy of Fallot.

PATENT DUCTUS ARTERIOSUS

The ductus arteriosus is a vascular channel connecting the pulmonary artery and the aorta. It represents an essential part of the fetal circulatory system. At birth, with the establishment of normal pulmonary circulation, it becomes useless, closes spontaneously and eventually becomes only a small strand of fibrous tissue between these two vessels known as the ligamentum arteriosum. When the ductus remains open after birth there is a reversal of the flow of blood through the ductus and it becomes an arterio-

* From the Journal of the Iowa State Medical Society 33: 85-88 (Mar.) 1918

venous fistula. The pressure being higher in the aorta than in the pulmonary artery, the shunt of blood is from the aorta to the pulmonary artery. The studies of Eppinger, Burwell and Gross have shown that in artificially created ductus arteriosus in dogs as much as 40 to 70 per cent of the total left ventricular output is shunted through the ductus to be recirculated through the pulmonary circuit. The circulatory dynamics will then result in a marked increased load on the left ventricle, a lessened systemic arterial blood flow in comparison to the cardiac work and an increased volume of pulmonary blood flow with consequent increased load on the right ventricle as well. With this concept in mind the clinical features of patent ductus arteriosus will be more clearly understood.

The patient is usually either a child, adolescent or young adult person who, not infrequently, is slightly underdeveloped and usually has been known to have a cardiac murmur since infancy or early childhood. There may have been no cardiac symptoms but dyspnea on exertion, undue fatigability and heart consciousness are common complaints. Emphasis should be placed on the fact that cyanosis is not associated with uncomplicated patent ductus until the onset of congestive heart failure. Subacute bacterial endocarditis is a common complication and, before the era of penicillin therapy, it caused 25 to 40 per cent of the deaths in cases of patent ductus. The lesion is one which is occasionally encountered in adult persons in middle age, but the studies of Bullock, Jones and Dolley have shown that in children with uncomplicated patent ductus arteriosus the life expectancy is markedly reduced; 50 per cent of the patients in whom the lesion was noted after the third year of life died before the thirtieth year of life. The principal finding on examination is the characteristic murmur of arteriovenous fistula which is a loud, continuous murmur, frequently described as a machinery type of murmur. There is systolic accentuation of the murmur. It is loudest in the second and third left interspaces where there is usually an associated thrill. The second pulmonic tone is accentuated and there may be an increased sharpness to the first tone at the apex. The murmur of ductus arteriosus is one of the few diagnostic murmurs and it is characteristic of this lesion. In infancy and again in patients with congestive heart failure the "ductus murmur" may be absent.

There is a wide pulse pressure with collapsing pulse similar to that seen in aortic insufficiency. This manifestation is the result of the physiologic effects of the arteriovenous fistula. In a typical case the blood pressure is in the neighborhood of 110 to 130 mm. of mercury systolic and 40 to 60 diastolic. The roentgenograms of the chest may reveal a heart which is essentially normal in size and in contour. In the majority of cases, however, one will note an increase in size of the left ventricle and a prominence of the pulmonary conus shadow. Roentgenoscopy will reveal an overactive left ventricle and, in most cases, increased pulsation in the pulmonary arterial shadows at the hilus of the lungs.

The electrocardiogram is an important link in the chain of evidence, principally because of the negative findings. The electrocardiogram usually reveals normal findings. If any abnormality is present it is that of a slight left axis deviation. The finding of right axis deviation in a suspected case of ductus arteriosus is almost certain evidence that there is some other associated anomaly. Since there is no venous arterial shunt in these cases

and no inadequacy of the pulmonary blood flow, the degree of oxygen saturation of the arterial hemoglobin will be normal until congestive heart failure occurs. Patent ductus arteriosus is one of the most easily recognized congenital cardiac anomalies and clinical diagnosis can be made with certainty in almost 100 per cent of the cases.

Surgical ligation or division of the ductus arteriosus has now become a relatively common operation. Six hundred and twenty-six cases have been reported and, no doubt, operations have been done in many more. The risk of surgical treatment has become progressively lower and is now less than 5 per cent in uninfected cases. In view of the ultimate poor prognosis in the untreated patient with patent ductus arteriosus it would seem only logical that at the present time surgical treatment be seriously considered in every case in which the diagnosis can be positively established. Although immediate surgical ligation has been advised by some authors in the infected case in which there is subacute bacterial endarteritis, it is my opinion that if the infective organism is one which is sensitive to penicillin, the infection should be eradicated by a prolonged course of penicillin therapy before surgical ligation is attempted.

TETRALOGY OF FALLOT

The combination of congenital defects known as the tetralogy of Fallot is one of the most interesting of cardiac anomalies. The clinical picture is well defined and an accurate diagnosis can usually be made. The anatomic derangement is primarily one of maldevelopment of the outflow track or the right ventricle and first portion of the pulmonary artery. The pulmonary artery is stenotic at the orifice or is small, narrow and underdeveloped. There is an associated defect in the membranous portion of the ventricular septum with overriding of the aorta, allowing both venous blood from the right ventricle and oxygenated blood from the left ventricle to enter directly into the aorta. The right ventricular enlargement, which completes the tetrad, is a secondary manifestation of the strain thrown on the chamber by the presence of the anatomic defects just mentioned. The tetralogy of Fallot in children beyond infancy is the most common congenital heart lesion associated with persistent cyanosis. There are numerous other more primitive defects of the morbus caeruleus type but with few exceptions they are incompatible with life for more than a few weeks or months. Although the average survival period of patients with tetralogy of Fallot is only twelve years, occasionally this lesion may be encountered in adult persons and one patient is known to have survived to his sixtieth year. This particular defect has gained wide interest as a result of the brilliant work of Blalock and Taussig, who were able to show that by increasing the volume of blood flow to the lungs by means of an artificial anastomosis between one of the systemic arteries, such as the subclavian or innominate, and the pulmonary artery, thus creating an artificial patent ductus arteriosus, the cyanosis and exertion tolerance of these children could be greatly improved.

Clinical Features of Tetralogy.—The clinical features of this syndrome are best illustrated in a child three to ten years of age in whom transient cyanosis was noted at birth or soon thereafter, particularly when the child was feeding or crying. The cyanosis becomes more severe or may first be manifest when the child becomes more active and capable of walking or

running. A murmur is usually present from infancy. It is systolic in time, loudest to the left of the mid-sternum, but there is nothing about the murmur which can, in any way, be considered diagnostic. As the child becomes older, cyanosis becomes more intense and physical activities become more severely restricted, with dyspnea and easy fatigability. After exertion commonly the child will assume a squat position to rest. This phenomenon is encountered so frequently in children with tetralogy of Fallot that it is believed to have some diagnostic importance. Sudden periods of unconsciousness in which the child becomes limp and intensely cyanotic are frequently noted.

With the persistent severe oxygen unsaturation of arterial blood caused by both the venous arterial shunt into the aorta and the marked deficiency in pulmonary blood flow, secondary polycythemia and clubbing of the fingers and toes become marked. It is not uncommon to find a hemoglobin content of 20 to 25 gm. or more per 100 c.c. of blood in these cases, a hematocrit reading of 70 or 80 per cent for erythrocytes and an oxygen saturation of arterial blood of 50 per cent or less.

The roentgenographic examination of the heart is of greatest value in making the diagnosis of tetralogy. The heart does not appear enlarged yet the rounding and elevation of the left lower margin of the heart away from the diaphragm indicates enlargement of the right ventricle. In contrast to the usual cardiac defects associated with right ventricular enlargement in which there is also a prominence of the pulmonary conus shadow, in tetralogy there is a concavity in this region. The combination of right ventricular enlargement with absence of the pulmonary conus shadow gives the heart a characteristic boot-shaped appearance, the so-called *cœur en sabot*. These findings will be noted more clearly on roentgenoscopic examination; in addition the pulmonary fields appear remarkably clear with absence of the usual arterial pulsations in the lung hili. The electrocardiogram shows evidence of a marked right axis deviation, a finding which is in no way diagnostic, inasmuch as most congenital heart lesions with persistent cyanosis in children, with the exception of tricuspid atresia, give the pattern of right axis deviation.

One must bear in mind that the objective in the surgical treatment of pulmonary stenosis is an attempt to increase the volume of pulmonary blood flow. This can be accomplished in two ways: (1) by the Blalock operation of anastomosing the subclavian artery on either side with the right or left pulmonary artery just beyond its bifurcation or (2) by making a direct side-to-side anastomosis between the aorta and pulmonary artery according to the method introduced by Potts, Smith and Gibson. Surgical treatment is not indicated in cases of congenital heart disease with cyanosis in which there is no deficiency in pulmonary blood flow. This imposes on the clinician a grave responsibility for the proper selection of cases. In children beyond the age of three years the most common lesion associated with cyanosis which may be confused with the tetralogy of Fallot is the Eisenmenger complex. The latter syndrome consists of a ventricular septal defect with overriding of the aorta but without pulmonary stenosis. In this lesion cyanosis tends to be less intense and to develop at a later period in life. The lesion is usually consistent with a better tolerance for exercise. On roentgenographic examination, instead of concavity in the base as in

tetralogy, the pulmonary conus shadow is full and there are normal or increased hilar pulsations indicative of an adequate pulmonary blood flow. If the clinical and roentgenologic findings are uncertain and the patient is of such an age as to allow cardiac catheterization, a more accurate determination of the pulmonary blood flow can be obtained by this procedure. If the determinations reveal a normal volume of pulmonary blood flow, such patients should not be considered as candidates for surgical treatment.

Complete transposition of the great vessels in which the aorta rises from the right ventricle and the pulmonary artery from the left ventricle represents a severe form of *morbus caeruleus* and is seldom compatible with life beyond a few weeks or months. In the rare case in which this lesion is encountered in children the clinical picture may closely resemble tetralogy of Fallot. There are these few differences, however. The heart in complete transposition tends to enlarge rapidly and has a peculiar globular configuration, and the fact that the aorta lies in front of the pulmonary artery makes it possible for this lesion to be diagnosed by roentgenographic methods.

The surgical treatment of tetralogy of Fallot does not alter the basic defects in the heart and can in no way be considered a curative procedure, which is in contrast to the effects of surgical treatment in patent ductus and in coarctation. The basic concept of the altered physiology, the proof of soundness of the idea of creation of an artificial ductus obtained through studies on animals and finally the successful employment of the procedure in the patient with tetralogy all represent one of the most outstanding surgical contributions in our time. All credit is due Blalock and Taussig for this splendid achievement. Even though questions regarding the ultimate prognosis in patients who have undergone surgical treatment and the question of added cardiac strain caused by the creation of the artificial ductus remain unanswered, there can be no question but that these children are greatly benefited by this type of operation. In light of the formidable nature of the procedure the surgical mortality will continue to be high, but yet, in those cases in which the operation is successful it may well be considered a lifesaving procedure.

The achievements in this field of vascular surgery in recent years have truly been remarkable and it would seem likely that we are witnessing now only the opening of a much greater field in which vascular surgery based on sound physiologic principles will be employed. It was not my intention to discuss the surgical aspects of the treatment of these lesions, but rather to acquaint you better with the clinical features associated with two of the lesions which at present may be benefited by surgical treatment.

INCOMPLETE DIVISION OF THE ATRIOVENTRICULAR CANAL WITH PATENT INTERATRIAL FORAMEN PRIMUM (PERSISTENT COMMON ATRIOVENTRICULAR OSTIUM): REPORT OF FIVE CASES AND REVIEW OF THE LITERATURE*

H. MILTON ROGERS AND JESSE E. EDWARDS

This paper is based on a report of five cases of the congenital cardiac disease termed incomplete division of the atrioventricular canal with patent interatrial foramen primum (persistent common atrioventricular ostium) and on a review of the essential pathologic and clinical features in an additional fifty cases reported in the literature. In the entire group of fifty-five cases, the median age of the patients at the time of death was ten months. More than half of the patients died before they were one year of age. Only five of the patients lived beyond the age of thirty years. The anomaly apparently does not have any predilection for either sex.

In the fifty-five cases, it appears that the lesion under consideration acts essentially as does a simple interatrial septal defect. Enlargement of the right side of the heart and widening of the pulmonary artery orifice are common associated secondary lesions. Cyanosis may be present at birth but is usually acquired. When this manifestation develops, it is a sign of failure of the right side of the heart, pulmonary disease or both. Cardiac murmurs, usually systolic, are frequently observed; they occurred in twenty-two of twenty-five cases in which an adequate history was given with reference to this sign.

Mongolism is a relatively common associated finding in cases of incomplete division of the atrioventricular canal with patent interatrial foramen primum. In those case reports in which there was an adequate history, mongolism was recorded as having been present in seventeen cases and its absence was recorded or could be assumed in eight cases.

Bacterial endocarditis was observed in three of the fifty-five cases.

(Since this manuscript was prepared we have observed a sixth example.)

CONTINUOUS OBSERVATIONS OF THE ARTERIAL OXYGEN SATURATION AT REST AND DURING EXERCISE IN CONGENITAL HEART DISEASE†

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(WITH THE TECHNICAL ASSISTANCE OF LUCILLE CRONIN)

Analysis of arterial samples from twenty resting persons with congenital heart disease has been used as a reference point for continuous measurements of the arterial oxygen saturation with the Millikan compensated circuit oximeter during exercise and other procedures. Nineteen normal volunteers were studied as controls. Observations have been made while

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† Abstract of paper published in full in the *American Heart Journal*. (In press.)

the individuals breathed pure oxygen, with and without positive pressure up to 4 inches (10.2 cm.) of water, while they stood upright, and while they walked on a power-driven treadmill at 1.7 miles (2.7 kilometers) per hour.

In normal persons at rest, oximeter readings indicated that the arterial saturation was increased by from 1 to 5 percentage points (mean 2.7) in an average time of 1.3 minutes when pure oxygen was breathed. Addition of positive pressure to the oxygen supply caused no further change in the oximeter reading.

In resting patients with cyanotic types of congenital heart disease the arterial oxygen saturation averaged 71 per cent, ranging from 45 to 91 per cent saturation. Oximeter readings were increased from 2.0 to 16.5 percentage points (mean 6.2) in an average time of 3.0 minutes when these patients breathed pure oxygen. When the oxygen was given with positive pressure, oximeter readings increased, on the average, an additional 1.6 percentage points.

The normal group showed no significant change in their arterial oxygen saturation when they assumed the upright position or when they exercised by walking on a treadmill at 1.7 miles per hour for 5 minutes. The oximeter readings of persons with cyanotic types of congenital cardiac defects decreased, on the average, 2.4 percentage points when they stood upright, and decreases ranging from 3.5 to 19.0 percentage points (mean 10.9) occurred when they walked on the treadmill at 1.7 miles per hour for an average time of 3.5 minutes.

Simultaneous arterial samples and oximeter readings obtained both at rest and during exercise in a smaller series of patients indicated that the saturation changes recorded by the oximeter were less than the changes found by the Van Slyke analysis of arterial blood. Nevertheless, use of the oximeter in these tests has proved a valuable objective adjunct in assessing the degree of dysfunction in such patients both before and after surgical corrective procedures have been attempted.

TRENDS IN THE TREATMENT OF VARICOSE VEINS FROM THE HISTORICAL AND PRACTICAL VIEWPOINTS*

FREDERICK L. SMITH

EXAMINATION

During the general examination in the clinical service, patients are sent to the section which is concerned with venous therapy for evaluation of varices of the lower extremities, if such are present. If the patient is nervous or excitable, a sedative agent such as phenobarbital is administered when the patient arrives in the section. The patient, properly prepared, is asked to ascend steps to an examining platform. The patient is examined for any abnormalities such as lipedema, nevi which suggest the possible existence of arteriovenous fistula or congenital cavernous hemangioma, lymphedema

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praecox, hernias of muscle sheaths, arterial diseases, erythromelalgia, thrombophlebitis, thrombo-angiitis obliterans, dermatitis, ulceration including typical stasis ulcers, malignant and ischemic ulcers, ulcus medicamentosum, ulcerative colitis and ulceration of fungous origin. The method of palpation and percussion, commonly known as the Schwarz test, is performed to determine the patency of the greater saphenous vein. This is accomplished by the physician's placing the fingers of the left hand over the fossa ovalis and the fingers of the right hand over the enlarged vein in the leg of the patient. A wave both ways in the column of blood indicates venous incompetency.

The lesser saphenous vein is examined by placing the patient in the supine position, elevating the limb, collapsing the veins, placing a tourniquet at the groin, grasping the popliteal arch or using a tourniquet at that level and requesting the patient to stand. Hand pressure or the tourniquet is then removed, and if the lesser saphenous vein is incompetent, blood will surge down the vein, after which the tourniquet in the groin is removed. Incompetent perforating vessels are observed when the tourniquets are in place in the groin with the veins collapsed: the patient stands and filling occurs immediately below the tourniquet. When evaluation is completed, the patient returns to the consultant, who notes the findings written in the history and after appraisal of the patient's general examination, refers him back for treatment if the clinical findings warrant.

TREATMENT

Position of the Patient for Injection Treatment.—The position of the patient for injection treatment should be the same as for examination, so that the patient is in the most convenient position for the physician. The patient is requested to mount the steps and stand on the treatment table, supporting himself by grasping the uprights of a $\frac{3}{4}$ inch iron pipe frame which extends upward 70 inches, has a width of 25 inches and a crossbar at the top, above the table. The table is 33 inches above the floor. The steps on the table are 10 inches wide, so that the patient has a good tread in descending. Guard rails can be used to assist in descent.

Test Dose.—Before the test dose of 0.5 to 1 c.c. of sclerosing solution is injected, the patient is asked if previous injections have been carried out and, if so, whether any untoward reactions occurred. If reactions did occur the physician who treated the patient previously is asked by wire for information. If reactions did not occur, injections are carried out. The ordinary varix is injected by means of a syringe of 2 to 4 c.c. capacity and a 26 gauge needle $\frac{3}{4}$ inch long. This needle is sufficient to enter any superficial incompetent vein. Spider-web types of vessels are injected satisfactorily by filling the syringe a quarter full of the solution of sodium morrhuate, shaking it to produce suds, and injecting the suds. The bubbles pass readily up the plexus in the skin. The needle is removed, the area is massaged, and a sterile pad is applied over the site of the puncture and the area treated.

Allergic Reactions to Test Dose.—These reactions occur within a few minutes to several hours after injection of the initial test dose. Erythema with intense pruritus appears, or possibly large urticarial wheals resembling active exacerbation of hives develop. The subcutaneous injection of 1 c.c.

of a 1:1,000 dilution of epinephrine usually causes the cutaneous manifestations to subside. Rarely, shock results in which the blood pressure decreases markedly; the patient becomes weak, sweats profusely and requires from a few minutes to three or four hours before recovery occurs. The aforementioned solution of epinephrine can be injected subcutaneously and intravenously and, in case of impending pulmonary edema, the administration of $\frac{1}{160}$ grain (0.00065 gm.) of atropine is advisable. Ninety-five per cent oxygen and 5 per cent carbon monoxide and a cardiac stimulant, such as caffeine or sodium benzoate, may be administered.

Systemic Reactions to Test Dose—The patient may feel faint or nauseated. This usually can be controlled by having the patient sit, lower the head, and then raise it against pressure. A whiff of aromatic spirits of ammonia usually suffices to induce deep breathing. On rare occasions, cramps in the back which interfere with respiration because of intercostal spasm frighten the patient and also the physician, if he is not aware of what is happening. The sacrolumbar plexus causes such spastic muscle reactions, if it is stimulated. Assurance to the patient and stroking of the patient's back for a couple of minutes relieve the condition. Vision has been reported to be affected. Hematuria is a rare occurrence.

Hospitalization.—If no allergic reaction occurs, a varicose-vein history sheet is made out and if surgical treatment is required, hospital forms also are made out and taken to the hospital assignment desk. If the patient is to undergo bilateral ligation of the greater or lesser saphenous veins, hospitalization of one night is recommended, during which the patient is exercised at least three to five minutes each hour during the following twelve to eighteen hours.

Ligation.—In the performance of operations, a surgical operating room is best adapted for the purpose. Regional block anesthesia is used as described by Seldon, who administers a 5 per cent solution of a local anesthetic agent (metycaine), using about 70 c.c. in different areas. A lower abdominal quadrant is infiltrated to block the iliac and lumbar inguinal nerves, and the region of the femoral vessels similarly is infiltrated to block the sensory fibers preparatory to operation. The dose at time of ligation is 3 c.c., in each extremity, of a 5 per cent solution of sodium morrhuate.

Injection.—The next day the patient reports to the treatment section. If considerable systemic reaction is manifested by nausea or malaise, nothing is done until the patient feels better. Reaction occurring in the extremity usually is observed to extend from the groin down onto the leg among 65 to 72 per cent of patients. From the lower point of thrombosis, local injection is commenced. An average of 2 to 4 c.c. of solution is injected each day. Occasionally injection is carried out in both the morning and afternoon, in which case 2 c.c. of solution is injected at each visit. In 1946 the average number of injections per patient was seven. The length of the patient's stay is ten to thirteen days after ligation.

COMPLICATIONS

In the carrying out of subsequent sclerosing treatments, extravascular injections are neutralized by the instillation of isotonic solution of sodium chloride in the area of the spill. With care, extravascular injections should rarely occur, but in spite of good technic, they occasionally happen. De-

bridement or excision may be required, depending on the extent of damage. Pulmonary embolism occurs rarely; the incidence is about one in every 685 patients treated. One death was recorded among nearly 11,614 patients treated. At the least sign of complications of the upper part of the respiratory system, the patient should be hospitalized and anticoagulant treatment should be started. Possibly deep venous ligation ought to be carried out, depending on circumstances in the individual case. Radiography does not always reveal the trouble, especially if the infarct is minimal at first. Several days may pass before a roentgenogram of the thorax shows anything; it may disclose nothing at all. To relieve clear-cut involvement, I have placed the patient in the Fowler position, strapped the chest to restrict its movement, and placed the patient in an oxygen tent containing 50 per cent oxygen, especially if the patient is cyanosed. Morphine sulfate is administered to slow respiration, and a sedative agent is administered by rectum to keep the patient in a semicomatose state for several days. These measures ensure the patient's quiet and freedom from worry, which are helpful not only to the patient but also to the physician in his management of the patient and his relations with relatives.

CONTRAINDICATIONS TO TREATMENT BY INJECTION AND BY COMBINED LIGATION AND INJECTION

Conditions which, if present, constitute contraindications to the treatment are: (1) any disease associated with a poor prognosis as to life, such as congestive heart failure and coronary sclerosis; (2) uncontrolled diabetes mellitus; (3) blood dyscrasias, except mild types of hypochromic anemia; (4) severe hyperthyroidism; (5) acute infectious diseases; (6) pregnancy, if sclerosing solutions contain quinine in any form; (7) abdominal tumor; (8) occlusive arterial disease in the affected extremity; (9) active cellulitis, lymphangitis, or pyogenic infections of the affected leg; (10) recent thrombophlebitis involving the deep veins of the thigh and veins of the leg, and (11) extreme obesity.

THE ROLE OF CHRONIC THROMBOSIS OF THE PORTAL VEIN AND ITS TRIBUTARIES IN THE SYNDROME OF SPLENIC ANEMIA*

MAVIS P. KELSEY, HAROLD E. ROBERTSON AND HERBERT Z. GITTIN

Thrombosis of the splenic and portal veins and splenic anemia, or Banti's syndrome, are often seen together in the same patient. Despite numerous investigations the causal interrelationships of the two processes are still not understood. The problem has assumed new importance now that some relief may be offered to patients so afflicted. Until recently the only corrective measures available for relief of portal congestion in these cases were splenectomy, omentopexy and injection of esophageal varices by means of the esophagoscope. Splenectomy is only partially effective, since it reduces

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the portal blood flow by only 20 per cent. The value of omentopexy and injection of esophageal varices has been equivocal at best and these procedures are rarely used. Most recent efforts to combat portal obstruction are by splenorenal and portaecaval anastomosis as advocated by Blakemore and Lord or by extensive gastric resection as described by Baronofsky and Wangenstein.

Splenic anemia, or Banti's syndrome, as Banti finally described it in 1910, was thought to be the result of an undiscovered infectious agent brought to the spleen by the arterial blood to produce splenomegaly and passing on to cause sclerosis in the splenic and portal veins and cirrhosis of the liver. The anemia and leukopenia were thought to result from depression of the activity of bone marrow by the toxic agent. The characteristic microscopic finding in the spleen was "fibro-adenia" or fibrosis of the pulp and malpighian bodies with retention of the normal glandlike structural appearance.

Several diseases, including Gaucher's disease, chronic hemolytic anemia and some forms of leukemia, have been segregated as specific entities from splenic anemia while dozens of suggestions have been advanced as to the etiology and pathogenesis of the remaining large number of unsolved cases. We can divide these suggestions into three groups, each with numerous variations. First is the suggestion, similar to that of Banti, that the spleen is involved primarily, the changes in the veins and liver occurring secondarily as a result of liberated toxins. Ravenna's idea of a primary active congestion in the spleen and Pemberton and Kiernan's idea of an intrasplenic arteriovenous shunt may be included in the first group. Second is the suggestion that the spleen has a secondary role. This considers the process either to be a simple obstructive, congestive splenomegaly or to be a concomitant manifestation of hepatic disease. Third, the most reasonable suggestion is that splenic anemia is a symptom complex common to a miscellaneous collection of diseases in which the spleen has either a primary or a secondary role. These diseases include splenoportal thrombosis, hepatic cirrhosis and chronic infectious splenomegaly.

Several important questions arise when one attempts to decide which of these assumptions is most tenable. What is the actual cause of the splenic and portal venous disease seen in many cases of splenic anemia or Banti's syndrome? It is important to know if these venous changes are secondary to toxins or thrombogenic agents liberated by the spleen, as first postulated by Banti, or if they result from causes completely unrelated to the spleen. If the causes are unrelated to the spleen, does the obstruction and congestion caused by chronic splenic and portal thrombosis produce the splenomegaly? For comparison, does the portal congestion encountered in cases of hepatic cirrhosis cause splenomegaly or does pure chronic passive congestion encountered in cases of prolonged heart failure cause splenomegaly? Finally, what is the incidence of portal congestion and what are its causes in cases in which the clinical diagnosis is splenic anemia?

METHOD

In an effort to answer these questions we have made a clinical and pathologic analysis of data on several groups of cases in which necropsy was performed. There were sixty-one unselected cases of chronic disease of the

splenic or common portal vein in which the disease had lasted six months or longer. One hundred consecutive cases of hepatic cirrhosis were divided into the following groups: twenty-six with intrahepatic portal obstruction, twenty-five without evidence of intrahepatic or other portal obstruction and forty-nine unsuitable for study owing to inadequate data or to the presence of other factors which influenced splenic size. Twenty cases of heart disease were selected in which the patient had died after two or more years of chronic congestive heart failure. There were thirty cases with the clinical diagnosis of splenic anemia which after pathologic study still met all the general criteria of Banti.

RESULTS AND COMMENT

Pathology of Chronic Disease of the Portal Veins.—No clinical or pathologic evidence was found to support the thesis of Banti that chronic disease of the splenic and common portal veins is caused by toxins liberated by the spleen. Instead, we found some other positive or probable cause for the chronic venous disease in forty-eight of the sixty-one cases. In most instances the cause was unrelated to the spleen. Even in seven of the fourteen cases in which a clinical diagnosis of splenic anemia had been made a well-established cause completely unassociated with the spleen could be found to account for the thrombosis.

There were some cases in which more than one cause was present. For example, several patients who had cirrhosis underwent surgical exploration which involved manipulation of the portal vessels. The surgical procedures were usually for disease of the biliary tract or the appendix but in one case persistent ascites developed two weeks after thyroidectomy and at necropsy two years later typical chronic thrombotic changes were observed in the portal veins. In nearly all cases of malignant lesions the growth had invaded the veins and secondary thrombosis had occurred. In several instances of disease of the biliary tract, inflammation was actually seen to spread from the common bile duct to the portal vein. Similar spread of inflammation to the veins was seen in cases in which duodenal ulcer or pancreatitis was present. Pylephlebitis is usually thought to be a rapidly fatal disease but one of these patients survived for eleven years after an acute phase of the disease to present a classic picture of splenic anemia. Pylephlebitis is probably a more frequent cause of chronic portal venous disease than is realized. Patients who have chronic congestive heart failure usually have an associated abdominal disease which also participates in the formation of thrombi. Omphalitis in infancy may account for many of the cases of splenic anemia appearing in early childhood.

Chronic progressive thrombosis was the most common type of pathologic change in the veins. There were thirty-nine such cases among the fifty-three in which microscopic sections were available. Without going into the controversy concerning pathogenesis of clot formation these lesions were predominantly thrombotic in twenty-eight cases and predominantly phlebitic in eleven.

The thrombotic vessels displayed an extremely chronic intimal thickening. Usually eccentrically placed and constricting or obliterating the lumen, the process arose from intimal proliferation and organization of thrombi. Canaliculi and deposits of iron were usually present to indicate the throm-

botic origin of this change. The media was thickened, showing a cellular response where there was overlying recent thrombosis. Muscle fibers were replaced in great part by fibrous tissue. The adventitia also was thickened by an abnormal amount of fibrous tissue and free cells. In the phlebitic group the process was predominantly inflammatory, characterized by polymorphonuclear cellular infiltration. Thrombotic clots were completely overshadowed by suppuration in two cases of protracted pyelphlebitis. In addition there were cases depicting all degrees between almost pure thrombosis and almost pure suppuration.

Eight cases fitted the often quoted descriptions of phlebosclerosis and were probably the result of ancient thrombosis as evidenced by scarring of the media and adventitia, the presence of canaliculi and iron deposits and the finding in proved thrombosis of venous segments which are identical to phlebosclerosis. Although there was no substantiating evidence, in some of these cases the changes may have been the result of developmental stenosis of the portal vessels.

The technical difficulties of vascular surgery and the fertile soil for post-operative thrombosis in most of the cases are obvious. The process was usually progressive with repeated thromboses superimposed one on the other and showed various stages of organization in different segments of the veins. Furthermore, in only a few cases was the disease limited to the splenic or the common portal vein; it usually extended to involve two or more major veins or into the smaller collateral veins, obstructing them and exaggerating the portal obstruction. Incidence of venous involvement was as follows: common portal, forty-six cases; splenic, forty-four; intrahepatic branches, forty-one; and mesenteric, twenty-three.

Cavernomatous transformation was a finding associated with both the thrombotic and the phlebosclerotic vessels and was interpreted as new-formed collateral circulation. Neoplastic obstruction was seen in five cases. In only one case, that of an eighty-two year old man, was there a small primary atherosclerotic obstruction which involved the splenic vein. Superimposed terminal thrombosis was seen in forty-three cases.

Splenomegaly in Chronic Splenoportal Venous Disease.—Of the sixty-one cases of chronic disease of the portal veins, forty-four were suitable to study the effect on the spleen of chronic venous obstruction. Seventy-three per cent of the spleens were enlarged and the mean weight was 685 gm., even though there was an extremely wide range. For those cases in which there was splenic enlargement no cause outside of venous obstruction could be found to account for the enlargement. Associated cirrhosis or toxemia of infection could have caused it in only a few cases. Why, then, were not all the spleens enlarged? Because several factors in addition to portal congestion influenced the size of the spleen. First, the presence of old infarcts with parenchymal destruction definitely prevented enlargement in two or more cases. One of these spleens weighed 35 gm. and was composed chiefly of scar tissue. Second, there tended to be less enlargement among the older patients, owing to their naturally diminished splenic function and blood flow. In three cases of complete splenic venous obstruction in which the patients were more than seventy-three years of age no collateral circulation, splenomegaly or other evidence of portal congestion developed. Third, in cases of minimal portal obstruction or well-developed collateral circulation

there was less enlargement. Fourth, and most important, was the duration of obstruction, for in eleven cases in which the duration could be reasonably determined to be less than two years the splenic mean weight was 215 gm. while in thirty-one cases in which obstruction had lasted for two years or longer, the mean weight was 310 gm.

The histologic appearance of the spleens in most of the cases was uniformly alike and was remarkably similar to that of so-called splenic anemia or Banti's syndrome. Fibrosis of pulp and malpighian bodies with retention of normal architectural structure was seen in both large and small spleens. Reticulo-endothelial hyperplasia and perimalpighian fibrosis were more common in the larger than in the smaller spleens.

Splenomegaly in Cirrhosis and in Heart Failure.—Cirrhosis of the liver when associated with portal congestion produces a high incidence of splenomegaly (mean splenic weight: 544 gm.). This is shown in 85 per cent of the twenty-six cases where definite evidence of intrahepatic portal obstruction was found. Portal congestion was determined in these cases by the history of gastro-esophageal hemorrhage and ascites and the presence of increased collateral circulation.

McIndoe pointed out that portal obstruction in cirrhosis results from derangement of the intrahepatic portal veins by growth of hyperplastic liver cells. The obstruction may be complete long before hepatic function is appreciably diminished, so that in some cases of mild cirrhosis there is severe portal congestion. This was true in five of these twenty-six cases. Four spleens were not enlarged in spite of distinct portal congestion and no cause was found to explain this. Contrary to Rousselot's opinion, the degree of obstruction did not always determine the degree of splenomegaly.

Histologic changes in the spleens in most of these cases were similar to, or identical with, those of chronic portal venous disease or splenic anemia.

In the twenty-five cases of cirrhosis in which no evidence of portal obstruction was found, the mean weight of the spleens was only 281 gm. The lack of obstruction in these cases may be explained in twenty cases by the slight degree of cirrhosis. Since severity of cirrhosis and severity of portal obstruction are usually of about the same degree it is difficult to determine whether the cirrhotogenous toxins acting on splenic parenchyma or the portal obstruction plays the principal role in splenomegaly. Apparently, as McMichael believed, both factors play a part. Histologically these spleens usually showed the early signs characteristic of splenic anemia. Some congestion was seen, although there was no evidence of it elsewhere in the portal system. Perhaps the short duration of the disease also played a large part in the lack of marked splenomegaly.

Congestive heart failure of long standing failed to produce appreciable splenomegaly (mean splenic weight: 194 gm.), even though the histologic changes were those of marked chronic passive congestion and often simulated the picture of splenic anemia. These findings seem to indicate that chronic passive congestion *per se* is not a cause of marked splenomegaly. Perhaps in order to cause splenomegaly the portal pressure must be higher than that produced by heart failure, the congestion must be active instead of passive or there must be a high differential between portal and systemic venous pressures.

Cases in Which the Diagnosis Was Splenic Anemia.—In the vast major-

ity of the thirty cases in which the clinical diagnosis of splenic anemia had been made portal congestion was present. From this group with congestion it will be seen that the surgeon may expect to find chronic venous disease in half the cases (14) and cirrhosis in almost as many (11). The fourteen cases in which there was venous disease have already been described among the sixty-one cases in which there was chronic disease of the portal veins. Many of those sixty-one cases were alike both clinically and pathologically whether diagnosed splenic anemia or not. Also in the group of 100 cases in which there was hepatic cirrhosis the cases with splenomegaly were similar to the eleven cases of splenic anemia with cirrhosis. As previously shown, histologic changes in the spleen are usually the same for splenic anemia, cirrhosis and chronic disease of the portal veins.

These findings indicate that the changes form a pattern which may appear in response to more than one cause. When cirrhosis or chronic portal venous disease is manifested clinically by splenomegaly, and by anemia and leukopenia as a result of secondary splenic overactivity, the diagnosis of splenic anemia is often made. It is easy to make a diagnosis based on such findings whereas it would be difficult to discover the underlying process.

In three instances of splenic anemia there was congestion with no apparent portal obstruction. These may be examples of a unique disease. The hypothesis of Pemberton and Kiernan that the portal congestion is a result of intrasplenic, arteriovenous shunt may explain these cases. Determinations, at the time of operation, of blood flow through the spleen may provide valuable information on this hypothesis. The two remaining cases of splenic anemia had no portal congestion or obstruction and demonstrate something we must not forget: that the syndrome of splenic anemia may be produced in an occasional patient by a cause other than portal congestion.

CONCLUSIONS

A well-established cause outside the spleen can be found to account for chronic disease of the splenic or portal veins in most cases. No evidence was found which indicated that toxins liberated by the spleen cause the venous disease.

The most common type of lesion in the veins in chronic disease of the portal vein is chronic thrombosis. In the cases of severe so-called phleboscclerosis the condition is the result of ancient thrombosis. Neoplastic invasion occurs in a few instances and atherosclerosis in a rare case.

In the majority, but not all, of the cases of chronic disease of the spleno-portal veins splenomegaly is associated. Several factors other than portal obstruction influence the size of the spleen in these cases. Those which tend to limit the degree of splenic enlargement are splenic infarction with parenchymal destruction, advanced age of the patient, well-developed collateral circulation and brief duration of the obstruction.

Cirrhosis of the liver often produces splenomegaly and the complete clinical picture of splenic anemia, but the pure chronic passive congestion of prolonged heart failure does not produce splenomegaly.

Splenic anemia is not a specific disease entity. The syndrome can be produced by a number of diseases; the most common are chronic spleno-portal thrombosis and hepatic cirrhosis.

MAINTENANCE OF VASODILATATION OF THE EXTREMITIES OF NORMAL INDIVIDUALS FOR A PROLONGED PERIOD BY THE INGESTION OF TWO TO FOUR SUBSTANTIAL MEALS IN CLOSE SUCCESSION*

GRACE M. ROTH AND CHARLES SHEARD

Since it has been shown by various investigators that there is a significant rise in the cutaneous temperature of the fingers and toes after the ingestion of a substantial meal, and a definite increase in the rate of blood flow (cubic centimeter per minute), the question arose as to whether the rise in cutaneous temperature of the fingers and toes could be maintained for an additional period by the ingestion of three or four successive substantial meals.

Thirty-five observations, each involving seven to eight hours, were made of the cutaneous temperatures of the extremities of twenty-four normal persons. For the most part, these persons had low basal metabolic rates and cold feet. In twenty-six observations, three successive meals were given; in nine, four successive meals were given; in two, two successive meals were given. In only four instances, with the first meal, was there no rise in the skin temperature of the extremities of those who ingested three meals, and in only one instance was there no significant rise in this temperature with ingestion of the first and second meal, but there was a definite rise after ingestion of the third meal. Two of the same persons who received four meals one day also received three meals on another day, and again there was no significant rise in temperature with the first meal. In general, a rise in the cutaneous temperature of the extremities could be produced and maintained for a period of seven to eight hours by means of ingestion of successive meals.

A CASE OF CHRONIC NEPHRITIS IN CHILDHOOD WITH LATER DEVELOPMENT OF SEVERE HYPERTENSION; RENAL BIOPSY†

EARL I. MULMED, ARCHIE H. BAGGENSTOSS AND HOWARD B. BURCHELL

A case of hypertension in a white man, twenty-nine years old, is reported. The patient had had glomerulonephritis at nine years of age which clinically had progressed to latent chronic glomerulonephritis. At the age of nineteen hypertension developed. Renal function remained good throughout the course of both diseases. Bilateral sympathectomy was performed and the result was satisfactory. Biopsy of the kidney and muscle confirmed the fact that diffuse arteriolar disease was present, but no evidence of chronic glomerulonephritis was observed.

* Abstract of paper published in full in the *American Journal of Physiology*, 152: 183-198 (Jan.) 1949.

† Abstract of paper submitted to the *Annals of Internal Medicine*.

CONDITIONS WHICH RESULT IN INCREASED PRESSURE WITHIN THE LESSER CIRCULATION*

C. ALLEN GOOD AND THOMAS J. DRY

Hypertension within the lesser circulation may arise under a variety of circumstances. Until the recent development of the procedure for catheterization of the heart, there was no practical method for measuring the pressure in the pulmonary circuit. Recognition of pulmonary hypertension depended, therefore, on a knowledge of the various mechanisms capable of producing it and on the recognition of the secondary phenomena resulting from its presence. Although new knowledge concerning pulmonary hypertension undoubtedly will be disclosed by catheterization, it is well to review the information which can be gained without resorting to this procedure.

Any mechanism which leads to increased pressure in the lesser circulation increases the work of the right ventricle. If this increased pressure persists, hypertrophy of the right ventricle results. Arteriosclerotic changes in the pulmonary arteries follow and over a period of time, when the reserves are exhausted, failure of the right side of the heart ensues. In certain conditions in which rapid development of pulmonary hypertension occurs, dilatation rather than hypertrophy of the right ventricle takes place. This change is reversible if the cause of the increased pressure is eliminated.

The signs of pulmonary hypertension which are disclosed to the roentgenologist are (1) enlargement of the pulmonary arteries and of the outflow tract of the right ventricle (conus) and (2) enlargement of the right side of the heart. If incompetence of the pulmonary valve is added because of dilatation of the right ventricle, the phenomenon of "hilar dance," an exaggerated pulsation of the pulmonary arteries in the hilus of the lung, also may be seen.

The sign which is present earliest is enlargement of the pulmonary artery and of the outflow tract of the right ventricle, the pulmonary conus. Usually the enlarged pulmonary conus can be seen as a convexity of the upper portion of the left border of the cardiac silhouette. In the right anterior oblique position this convexity is more marked and this portion of the heart shadow may bulge into the retrosternal space.

In addition to enlargement of the conus the branches of the pulmonary artery in the hilus of the lung may appear dilated. Schwedel stated that the descending branch of the right pulmonary artery normally measures between 9 and 14 mm. in diameter. These figures apply only if teleroortogenograms are employed and the artery is measured in its upper portion perpendicular to the bronchus which defines its medial border.

Enlargement of the right ventricle usually appears on the postero-anterior roentgenogram of the thorax as enlargement of the heart shadow to the left. The diaphragmatic segment of the heart is found, in the left anterior oblique position, to be increased in size and its ventral border is rounded. Enlargement of the left ventricle will, in this position, produce a rounding of the dorsal border of the cardiac shadow. As enlargement

* Read at the meeting of the American Roentgen Ray Society, Atlantic City, New Jersey, September 17, 1947.

progresses the tricuspid valve may become incompetent and the right auricle may become dilated; this produces enlargement of the heart shadow to the right.

In a typical case the roentgenologist will see a convex left border of the heart possibly with some enlargement of the cardiac silhouette. The aortic knob may be less prominent than usual because of rotation of the heart on its vertical axis, and the hilar vessels may be dilated.

CAUSES OF PULMONARY HYPERTENSION

The various conditions which cause pulmonary hypertension may be classified into the following groups: (1) obstruction to the lesser circulation beyond the pulmonary circuit, (2) obstruction within the pulmonary system, (3) abnormal shunts of blood from the arterial side into the pulmonary circulation and (4) kyphoscoliosis.

Obstruction beyond the Pulmonary System.—The two most common causes of pulmonary hypertension due to obstruction beyond the pulmonary system are mitral stenosis and a failing left ventricle for any cause. In either instance the vessels of the lesser circulation are overloaded and the efferent blood stream from the lungs is impeded. In some cases of mitral stenosis arteriosclerotic changes develop in the arterioles of the lesser circulation, which further adds to the burden placed on the right side of the heart.

In addition to the enlargement of the conus, as seen on the roentgenogram, mitral stenosis produces enlargement of the left auricle. This can best be demonstrated roentgenologically by the posterior displacement of the barium-filled esophagus with the patient in the right anterior oblique position.

Obstruction within the Pulmonary System.—Within the pulmonary circuit the lesser circulation may be obstructed at different levels. The main pulmonary vessels may be occluded by an embolus or a thrombotic process. The small and medium-sized branches of the pulmonary arterial tree may become occluded in the course of sickle cell anemia, schistosomiasis or extensive metastatic carcinomatosis. The pulmonary arterioles may become sclerotic or they may undergo obliterative changes in association with many pulmonary diseases. Finally, the capillary system may be obstructed in emphysema and in widespread pulmonary fibrosis such as that found in tuberculosis and pneumoconiosis.

Shunts.—Abnormal shunts of blood from the arterial side into the lesser circulation are usually congenital but may be acquired. The most common congenital lesions of this type are patent ductus arteriosus, interatrial septal defect and Lutembacher's syndrome (interatrial septal defect and mitral stenosis). Rarely a shunt may be acquired by the gradual rupture of an aortic aneurysm into the pulmonary artery.

Kyphoscoliosis.—Kyphoscoliosis probably causes pulmonary hypertension because the thoracic deformity produces areas of atelectasis and of emphysema in the lung. It is a well-known fact that most hunchbacks die of heart failure. Bachmann has shown that in eighty-seven out of 154 cases death was due to failure of the right side of the heart.

A condition which produces pulmonary hypertension and one in which an early roentgenologic diagnosis is often extremely important is pulmonary embolism. In many cases of pulmonary embolism the clinical features are

so typical that roentgenologic aid is unnecessary. In others, particularly in those in which the clinical features are minimal or misleading, the roentgenologic signs may be of inestimable aid in arriving at a proper diagnosis.

Westermarck has stated that the roentgenologic sign of pulmonary embolism unaccompanied by infarction is a decreased density of the segment of lung supplied by the occluded artery. This appearance is due, he has said, to the lack of blood in that portion of the pulmonary arterial tree.

In many instances the roentgenologist may see the signs of acute cor pulmonale (fig. 55). These are dilated pulmonary vessels in the hilus, enlarged conus shadow and enlarged heart. It is probable that the sudden change in pressure in the lesser circulation is due to generalized spasm of the arterioles of the lung as well as to occlusion of a larger vessel. At any



Fig. 55a. Before operation. The size and shape of the heart and pulmonary arteries are normal. b. Fourteen days after cholecystectomy and one day after the onset of pain in the right side of the thorax. Signs of acute cor pulmonale are seen in the dilated pulmonary arteries, enlarged heart and convex upper segment of the left border of the cardiac shadow. The patient died a few hours after this roentgenogram was made. An embolus in the right pulmonary artery was found at necropsy.

rate, if the patient survives, canalization of the occluded artery takes place and the pulmonary hypertension subsides. Eventually the heart and pulmonary vessels return to normal size.

It is well to point out here that a roentgenologic diagnosis of pulmonary embolism based on the signs of pulmonary hypertension is often possible before the roentgenologic signs of pulmonary infarction and of pleural reaction appear. In such cases therapeutic measures can be instituted earlier, a feature which may save the life of the patient.

SUMMARY AND CONCLUSIONS

Pulmonary hypertension is a secondary manifestation of a wide variety of conditions which exert their effects either by obstruction of the lesser circulation in or beyond the pulmonary circuit, or by shunts of arterial blood into the pulmonary circulation. Regardless of the mechanism responsible for its production, pulmonary hypertension is recognized by the secondary effects on the cardiorespiratory system eventuating in right

ventricular hypertrophy or dilatation, changes characterized roentgenologically by enlargement of the pulmonary artery and conus. Absence of enlargement of the left auricle is evidence that the obstruction is within the pulmonary circuit.

Early diagnosis of pulmonary embolism, especially in those cases in which minimal or misleading clinical features occur, is possible by the recognition of the roentgenologic signs of acute cor pulmonale.

THE USE OF DICUMAROL AS AN ANTICOAGULANT: EXPERIENCE IN 2,307 CASES*

EDGAR V. ALLEN, EDGAR A. HINES, JR., WALTER F. KYALE AND
NELSON W. BARKER

Six years have elapsed since the first report on the clinical use of dicumarol. Since that time there have been a number of clinical reports by ourselves and others. The literature has been reviewed previously. It is the purpose of this presentation to consider this new therapeutic tool in the light of six years' experience.

Dicumarol is a pure chemical compound which may be recovered from spoiled sweet clover and which has been prepared synthetically. The discovery that it is the agent which causes spoiled sweet clover disease of animals which is characterized by hemorrhage, the determination of its chemical formula, the synthesis of it and other studies by Link and his associates mark an epoch in research which is admirably presented in the Harvey lectures for 1943-1944. Dicumarol impairs coagulation of the blood, *in vivo*, by depressing the values for prothrombin. When used clinically it has no other significant effect, except that hemorrhage may result when the concentration of prothrombin in the blood is diminished too greatly. Dicumarol is not an ideal anticoagulant because its effect is delayed for one to two days after oral administration, because its effect persists for several days after discontinuance of administration and because judicious use requires the services of skilled and experienced laboratory personnel. Heparin, the only other anticoagulant available for clinical use, has the advantage of quick action (within a few minutes after intravenous injection) and quick cessation of action (about three hours after injection). A further advantage is the satisfactory administration of it without "laboratory control." The disadvantages of use of heparin are the relatively great cost and the need for parenteral administration.

Heparin and dicumarol are not competitors for clinical use; the use of one complements the use of the other. In many instances they should be used together. Heparin should always be used when an anticoagulant effect is needed quickly and when reliable laboratory determination of the value for prothrombin in the blood is not available. Although it may be given by continuous administration, the intravenous injection of 50 mg. of heparin (5 c.c. of solution) every four hours has been satisfactory for clinical use.

* From the *Annals of Internal Medicine* 27:371-381 (Sept.) 1947.

Dicumarol should be used whenever an anticoagulant effect is needed over a period of days, weeks, months or years, and whenever there can be reliable determination of the value for prothrombin in the blood. When both a rapid and a prolonged effect of an anticoagulant are desired, heparin and dicumarol should be administered simultaneously; administration of heparin should be discontinued when dicumarol has produced a satisfactory effect on prothrombin.*

THE DOSAGE OF DICUMAROL

The amount of dicumarol to be used depends entirely on the value for prothrombin in the blood after the drug has been administered on two successive days. In our studies we have attempted to maintain the values for prothrombin in the blood between 10 per cent and 30 per cent, since our experiences have indicated that significant hemorrhage seldom occurs when the value for prothrombin in the blood is more than 10 per cent and that intravascular thrombosis seldom occurs when the value for prothrombin is less than 30 per cent. It is possible that dicumarol may be administered with satisfactory results if the value for prothrombin in the blood is not reduced as much as we have indicated.

The inexperienced may be confused by the use of the terms "prothrombin time" and "prothrombin percentage"; they do not have the same significance nor do they have a linear relationship. The laboratory should furnish to the clinician a chart by means of which he may convert prothrombin time into prothrombin percentage. According to the technic used at the Mayo Clinic, a normal prothrombin time is seventeen to nineteen seconds; a prothrombin time of twenty-seven seconds signifies 30 per cent prothrombin; thirty-five seconds signifies 20 per cent prothrombin and fifty-eight seconds indicates 10 per cent prothrombin. However, in other institutions where different thromboplastins or techniques are used in the performance of the prothrombin time test, quite different prothrombin times may correspond to values for 100 per cent, 30 per cent, 20 per cent and 10 per cent prothrombin.

Three hundred milligrams of dicumarol are given on the first day and 200 mg. on the second day. On each subsequent day when the prothrombin is more than 20 per cent, 200 mg. are given. On any day when the value for prothrombin is less than 20 per cent, dicumarol is withheld. There are minor variations of this program depending on sensitivity or resistance of a patient's prothrombin to dicumarol, which have been discussed in another publication.

THE DANGER OF HEMORRHAGE WHEN DICUMAROL IS USED

The sole danger associated with the use of dicumarol is hemorrhage. In our series of 1,983 postoperative cases minor hemorrhage (epistaxis, hematuria and localized ecchymosis) occurred in 3.4 per cent of cases and serious bleeding (from operative wounds or from the gastro-intestinal tract) occurred in 1.8 per cent of cases. One may expect minor bleeding in about one of each twenty-five postoperative cases and serious bleeding in about

* When both heparin and dicumarol are used, blood for determination of the values for prothrombin should be drawn not less than three hours after the last injection of heparin, since heparin itself modifies the result of the test for prothrombin.

one of each fifty postoperative cases. There is a great difference between serious bleeding and fatal bleeding. Although marked bleeding from operative wounds occurred about forty times during the course of treatment of almost 2,000 patients who had undergone operation, death from hemorrhage occurred only twice. Careful study of the records of these two fatalities, reported in detail elsewhere, indicates that the fatal hemorrhage could not definitely be attributed to the effect of dicumarol. However, the two fatalities emphasize the ever-present danger of hemorrhage when dicumarol is used.

THE PREVENTION AND CONTROL OF HEMORRHAGE

The best method of preventing hemorrhage is to use dicumarol expertly. Even then, hemorrhage will occur. When epistaxis, hematuria and local ecchymosis are minor we do not ordinarily alter dosage but observe the patient for signs of more extensive bleeding. If bleeding from an operative wound is continued or marked, synthetic vitamin K (menadiol bisulfite) should be administered intravenously in amounts of 60 mg. and transfusion of fresh blood should be used to restore the blood that has been lost. The injection of vitamin K can be repeated at two hour intervals, once or twice as needed.

CONTRAINDICATIONS TO THE USE OF DICUMAROL

We use dicumarol cautiously or refrain from its use in renal insufficiency, which prolongs and enhances the effect of dicumarol, after operations on the brain or spinal cord because bleeding in these regions might result in disaster, in blood dyscrasias with increased tendency to bleed because dicumarol will accentuate the tendency to bleed, in ulcerative lesions because of the tendency to bleed, and in nutritional deficiencies or hepatic diseases associated with potential or actual prothrombin deficiency. We doubt whether the use of anticoagulants adds anything to the treatment of subacute bacterial endocarditis and we do not use them in such cases, since the danger of hemorrhage is relatively great.

EXPERIENCE IN 2,019 POSTOPERATIVE CASES*

The results of treatment in 352 cases of postoperative venous thrombosis are shown in table 1. In 832 cases of abdominal hysterectomy dicumarol was given prophylactically (table 2) because experience has indicated that in 4 per cent of such instances venous thrombosis occurs following operation; death from pulmonary embolism occurs in 0.7 per cent. In 329 cases of pulmonary embolism after operation anticoagulants were used (table 3). In addition to the cases considered in tables 1, 2 and 3, there were 470 instances in which dicumarol was used prophylactically to prevent pulmonary embolism and venous thrombosis. These were instances in which venous thrombosis or pulmonary embolism had occurred after previous operations or in which the prospects of postoperative venous thrombosis were considered relatively great. Venous thrombosis occurred in two instances. There was no pulmonary embolism. In thirty-six additional cases

* In many instances of pulmonary embolism, heparin and dicumarol were used. In most instances of venous thrombosis, dicumarol alone was used. In all instances in which an anticoagulant was used prophylactically, dicumarol only was used.

TABLE 1
RESULTS OF USE OF ANTICOAGULANTS IN 352 CASES
OF POSTOPERATIVE VENOUS THROMBOSIS

	Cases	
	Expected if anti-coagulants had not been used*	Occurred
Subsequent venous thrombosis or pulmonary embolism	88	9†
Fatal pulmonary embolism .	20	0

* On the basis of the rates given in the reports of Barker, Nygaard, Walters and Priestley.

† In 3 cases the percentage of prothrombin in the blood was more than 30. In 1 case use of dicumarol had been discontinued and prothrombin was normal

TABLE 2
RESULTS OF PROPHYLACTIC USE OF DICUMAROL IN 832 CASES
OF ABDOMINAL HYSTRECTOMY

	Cases	
	Expected if anticoagulants had not been used	Occurred
Venous thrombosis or pulmonary embolism. . .	83	3*
Fatal pulmonary embolism.	6	0

* Minor venous thrombosis.

TABLE 3
RESULTS OF ANTICOAGULANT THERAPY IN 329 CASES OF PULMONARY EMBOLISM

	Cases	
	Expected if anticoagulants had not been used	Occurred
Subsequent venous thrombosis or pulmonary embolism.	144	3
Fatal pulmonary embolism	60	1*

* Occurred after prothrombin time had returned to normal.

dicumarol was used prophylactically after amputation of a leg because of arteriosclerosis obliterans or thrombo-angitis obliterans; there were no vascular complications except that bleeding into the region of amputation occurred in one instance. Unfortunately no figures are available for comparison of results with and without anticoagulants. We can indicate only that dicumarol provided adequate protection against venous thrombosis in these cases.

An over-all consideration of the 1,513 cases presented in tables 1, 2 and 3 indicates that the following results were achieved: eighty-five patients survived who might have been expected to die had anticoagulants not been used, 250 patients were spared venous thrombosis or nonfatal pulmonary embolism. No great accuracy is claimed for these figures since alternate patients were not treated with and without anticoagulants; the control figures were calculated from experiences before anticoagulants were used. We recognize the deficiency in this method of study but the striking efficiency of anticoagulants in preventing pulmonary embolism and venous thrombosis is nonetheless impressive.

ADDITIONAL DISADVANTAGES OF ANTICOAGULANT THERAPY

In considering venous thrombosis and pulmonary embolism there is one most desirable goal—absolute prevention. This has not been achieved. Table 2 illustrates the point well. Eight hundred thirty-two patients who had undergone abdominal hysterectomy were treated with dicumarol in order to save six lives and in order to prevent venous thrombosis and nonfatal pulmonary embolism in thirty instances. The returns might be considered small. The numerical results are more impressive in cases of venous thrombosis and nonfatal pulmonary embolism; yet it was necessary, in the aggregate, to treat 681 patients in order to save seventy-nine lives and to prevent further venous thrombosis and embolism in 220 instances. We do not belittle these results. We only emphasize our inability to detect the predisposition to venous thrombosis *before it occurs*. Were it possible to designate the patients who would have venous thrombosis *before they had it*, treatment with anticoagulants would be even more productive. There has been a good deal of study on this phase of the problem of venous thrombosis and embolism; some progress has been made on the periphery but the hard core of the problem remains.

COMMENTS ON LIGATION OF VEINS VERSUS USE OF ANTICOAGULANTS

Our experience with ligation of veins has been very limited. That is a natural result of the gratifying experiences with anticoagulants that we have had. Furthermore, we do not know of any results from ligation of veins which approach in excellence those derived from our experience with anticoagulants. It is well to remember that the sole purpose of ligation of veins is to prevent pulmonary embolism. Also ligation of a vein will prevent pulmonary embolism only from that region which is distal to the ligature. Thus if the surgeon ligates the left superficial femoral vein he will prevent pulmonary embolism only from the left leg distal to the ligature. It is common experience that in such instances pulmonary embolism may originate from the right leg or from a region proximal to the ligature on the left.

Anticoagulants are used for two purposes—to prevent pulmonary emboli from originating anywhere in the body and to prevent extension of venous thrombosis. While it is more impressive to prevent pulmonary embolism, the importance of preventing occurrence or extension of venous thrombosis must be stressed. Any physician, observing the varices, edema, stasis dermatitis and cellulitis, and varicose ulcers years after a patient has had postoperative venous thrombosis, can testify to that. There is some difference of opinion in surgical circles as to whether or not ligation of veins contributes to the chronic venous insufficiency which might ordinarily result from venous thrombosis. Certainly ligation does not lessen venous insufficiency as anticoagulants do by preventing extension of the thrombosis.

Our carefully considered opinion, after weighing available evidence, is that the use of anticoagulants is, in general, a much better method of treatment than ligation of veins. We recognize a small role for ligation of veins, which is, at times, quite important, but we do not recognize superiority of this method in the type of case which has been considered in this presentation.

ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION

Three previously published reports by others indicate the usefulness of anticoagulants in acute myocardial infarction. Fifty patients who had this condition have been treated at the clinic; the detailed report by Parker and one of us is available elsewhere. One hundred cases observed at the clinic previously, before the use of anticoagulants, served as the control series. In ten of our cases heparin and dicumarol were used; in forty cases dicumarol alone was used. There were no instances of peripheral arterial embolism or venous thrombosis. Pulmonary embolism which did not cause death occurred in one instance (2 per cent) at a time when the prothrombin in the blood was not satisfactorily reduced. Five patients died (10 per cent). Evidence of further myocardial infarction occurred in one instance (2 per cent). There was only one instance of serious bleeding, hemarthrosis of a knee joint. In the control group the incidence of pulmonary embolism, peripheral arterial embolism and venous thrombosis was 33 per cent, the incidence of further myocardial infarction was 15 per cent and the death rate was 13 per cent.

No final conclusion can be drawn from experience with fifty cases nor from the other individual reports. However, in the aggregate the results seem significant. Certainly there is no evidence of harm resulting from the use of anticoagulants in acute myocardial infarction. Final decision relative to the value of this type of treatment must wait on extensive experience with a large number of cases, such as that now being obtained by a co-operative study under the supervision of Dr. I. S. Wright and the American Heart Association.

We believe that both heparin and dicumarol should be used in the treatment of acute myocardial infarction, that treatment should be begun as soon as possible after the diagnosis has been made and that it should be continued for at least four weeks.

ANTICOAGULANTS IN THE POSTPARTUM STATE

Previous reports indicate that dicumarol may be used safely and with benefit in the treatment and prevention of venous thrombosis following

delivery. Indeed the first dose may be administered prophylactically during labor and administration may be continued during the postpartum state without inducing uterine hemorrhage. Dicumarol may appear in the milk of lactating animals to which it is given; indeed baby rats nursing from mothers receiving dicumarol may bleed and die. However, the dose (5 mg. daily) given to the mother rats produced prothrombin deficiency in their blood and caused them to die in six to nine days. The dose administered to the rats was many times greater than that given to patients, if body weight is considered. No conclusions can be drawn from these studies except that if rats are given excessive amounts of dicumarol, their milk may contain sufficient dicumarol to produce profound prothrombin deficiency in nursing young. There is no clinical corollary to this situation.

We have administered heparin and dicumarol or dicumarol alone to nineteen postpartum patients, *four* of whom had pulmonary embolism and *fifteen* of whom had venous thrombosis in the legs. Four of these patients had undergone cesarean section. Treatment was begun as early as the fifth postpartum day to patients who had vaginal delivery and as early as the eleventh day following cesarean section. There was no unusual bleeding although the values for prothrombin in the blood were mostly between 10 per cent and 30 per cent after the third day of treatment. In no instance was there further venous thrombosis or pulmonary embolism. Only two mothers were nursing their babies while they received dicumarol. Repeated studies of the blood of each baby indicated that the values for prothrombin were never reduced significantly; they were consistently between 90 per cent of normal and normal, even when the values for prothrombin in their mothers' blood were between 10 per cent and 30 per cent.

Our studies support the conclusions of previously published reports that anticoagulants may be used after delivery, as needed for the prevention and treatment of pulmonary embolism and venous thrombosis. The problem of prothrombin deficiency of babies induced by dicumarol in mothers' milk cannot be considered wholly settled, although prothrombin deficiency did not occur in our two cases. When dicumarol is given to a mother who is nursing a baby, it is probably the course of wisdom to give the baby vitamin K or to determine values for prothrombin in the baby's blood and to correct any deficiency of prothrombin which may occur.

EXPERIENCE WITH MEDICAL PATIENTS

A group of 288 patients who had various kinds of vascular diseases have been given dicumarol as part of their program of medical treatment. A summary of the diseases from which these patients were suffering and the results of anticoagulant treatment is given in table 4.

The three large groups consisting of those who had thrombophlebitis, pulmonary embolism or acute arterial occlusion are worthy of more detailed consideration.

Thrombophlebitis.—In this group were 138 patients. The thrombophlebitis was of the idiopathic type (one episode) in forty-two cases and of the recurrent idiopathic type (several episodes) in twenty-seven. In sixteen cases the thrombophlebitis followed trauma, in eight it was associated with acute infections, in eight with carcinoma, in five with blood dyscrasias, in four with thrombo-angiitis obliterans and in eleven with miscellaneous con-

ditions which may cause thrombophlebitis. In seventeen cases the thrombophlebitis occurred in varices including incompetent greater and lesser saphenous systems.

In ninety cases the thrombophlebitis involved the iliofemoral or deep sural veins or both.

The chief reason for giving dicumarol was to prevent pulmonary embolism and further venous thrombosis. There is no reliable information available as to the incidence of subsequent pulmonary embolism or venous thrombosis among patients who have thrombophlebitis which does not follow operation but it is reasonable to assume that it may be about as high as in the group of patients who have iliofemoral or sural thrombophlebitis following operations.

In this group fatal pulmonary embolism did not occur; two patients had nonfatal pulmonary embolism, during adequate prothrombin deficiency.

TABLE 4

RESULTS OF TREATMENT OF 233 MEDICAL PATIENTS WITH DICUMAROL

Condition treated with dicumarol	Total patients treated	Subsequent fatal pulmonary embolism	Subsequent nonfatal pulmonary embolism	Subsequent venous thrombosis
Thrombophlebitis .	138	0	2	4
Pulmonary embolism .	41	0	1	0
Sudden arterial occlusion. . .	45	0	0	0
Thrombo-angitis obliterans	23	0	0	0
Arteriosclerosis obliterans .	17	0	0	0
Miscellaneous*	21	0	0	0
Totals	233	0	3	4

* Includes patients who had chronic venous insufficiency, congestive heart failure, simple arterial thrombosis, cerebral thrombosis and other diseases.

In four cases subsequent venous thrombosis developed. In one of these cases it occurred after the administration of dicumarol had been discontinued because of difficulties in obtaining blood for prothrombin determinations and after the prothrombin value had returned to normal; in another the venous thrombosis occurred when the prothrombin value was greater than 30 per cent. In the two remaining cases there was adequate prothrombin deficiency at the time of the development of the venous thrombosis.

Pulmonary Embolism.—There were forty-four patients in this group. The incidence of subsequent pulmonary embolism and venous thrombosis without anticoagulant therapy among medical patients who have iliofemoral or sural thrombophlebitis is unknown but it probably is the same as that noted among patients after operation. In the group of medical

patients with pulmonary embolism now being considered, who were treated with dicumarol, there was no subsequent fatal pulmonary embolism or venous thrombosis; one patient had another nonfatal pulmonary embolism when the prothrombin value was between 20 and 30 per cent.

Acute Arterial Occlusion.—A more detailed report of our experience with the use of anticoagulants in the treatment of acute arterial occlusion has been given elsewhere. The results of the use of anticoagulants in the treatment of fifteen of the forty-five patients on whom we are reporting data was recorded in that report.

We have treated, now, acute arterial embolism in nineteen cases and acute arterial thrombosis in twenty-six cases with anticoagulants. The plan of treatment has included the use of dicumarol with a period of preliminary heparinization. The patients have been divided into two groups: those whose treatment was instituted early (within twenty-four hours) and those whose treatment could not be started until more than twenty-four hours had elapsed from the time of the occlusion. In the group of eleven cases of acute arterial embolism in which treatment was started early, there was survival of the extremity in ten (91 per cent). In the group of eight cases in which treatment was late, the extremity survived in only two (25 per cent).

In the group of sixteen cases of acute arterial thrombosis with early treatment, the extremity survived in thirteen (81 per cent) whereas in ten cases with late treatment the extremity survived in five (50 per cent). These data indicate that when anticoagulant therapy is used in conjunction with other methods of emergency treatment one may expect survival of the extremity in a large number of cases if the treatment is started soon after the occlusion has occurred.

Incidence of Bleeding.—Two patients bled from the gastro-intestinal tract and one had severe subcutaneous bleeding. Treatment was discontinued in all instances. All patients recovered. Minor bleeding (epistaxis, hematuria and petechiae) occurred twice. Treatment was continued in all instances. The incidence of bleeding (1.0 per cent for major bleeding and 0.66 per cent for minor bleeding) was markedly less than the incidence noted in the postoperative cases considered earlier in this presentation.

Duration of Administration of Dicumarol.—The use of dicumarol in a group of patients with occlusive arterial disease who required treatment over a long period gave us the opportunity to observe the effect of prolonged administration of dicumarol in a small group. In forty-one cases dicumarol was given for as long as one month, in twenty-five for two months, in nine for three months, in three for six months and in one for ten months. No conclusion could be reached relative to the effectiveness of anticoagulants in the chronic occlusive arterial diseases. No untoward effects which might have resulted from the prolonged administration of the drug were observed in any of the cases. The prothrombin activity returned to normal in all within a few days after the administration of the drug was discontinued.

CONCLUSIONS FROM EXPERIENCE WITH MEDICAL PATIENTS

Our experiences indicate clearly that the anticoagulants are effective in the treatment and prevention of vascular thrombosis of medical patients just as they are effective in the care of postoperative patients with these

conditions. Fatal pulmonary embolism can be prevented and venous and arterial thrombosis can be halted in most instances. Early treatment of sudden arterial occlusion with anticoagulants and other measures results in survival of the extremity in 90 per cent of instances of embolism and 80 per cent of instances of thrombosis.

SUMMARY

1. The expert use of the anticoagulants, heparin and dicumarol, has improved tremendously the outlook for patients who have acute vascular thrombosis.

2. An over-all consideration of 1,513 postoperative patients treated with anticoagulants indicates that the following results were achieved: eighty-five patients survived who would have been expected to die from pulmonary embolism; 250 patients were spared venous thrombosis or nonfatal pulmonary embolism. In 506 additional postoperative cases in which dicumarol was used prophylactically, venous thrombosis occurred in but two instances; there was no pulmonary embolism.

3. A consideration of 298 medical patients indicates that fatal pulmonary embolism was prevented by anticoagulants. Nonfatal pulmonary embolism and venous thrombosis occurred very infrequently.

4. A study of fifty cases of acute myocardial infarction indicates substantial reduction in the incidence of further myocardial infarction and in arterial embolism and venous thrombosis.

5. Survival of the extremity occurs in 91 per cent of cases of arterial embolism and in 81 per cent of cases of arterial thrombosis, if treatment with anticoagulants is begun early and supplemented by other treatment.

6. In general, the use of anticoagulants constitutes the greatest contribution to the successful treatment and prevention of intravascular thrombosis and embolism.

THE CLINICAL USE OF ANTICOAGULANTS*

EDGAR V. ALLEN

A simple consideration indicates that if blood did not possess the quality of coagulation, even minor injuries would allow it to leak out of the body as freely as water flows through a sieve. This knowledge, which is possessed by every physician, has dominated medical thinking about coagulation of the blood. A vast proportion of the efforts of physicians has been devoted to making blood clot better, because of observation of the consequences which result from poor clotting of blood. There are few physicians who have not wished for a simple and efficient method by which they might stop bleeding.

It is quite clear now that thoughts of the medical profession must be turned in the reverse direction; there may be great benefits if blood clotted less well. It is doubtless true that hemorrhage causes many fewer deaths

*Abridgment of paper published in full in the *Cincinnati Journal of Medicine*, 28 375-381 (Sept.) 1917.

than intravascular thrombosis. When the blood vascular system is intact, coagulability of the blood may be reduced substantially without harm and, indeed, with benefit. It may be well to remark parenthetically that nature provides in abundance, even in excess. Thus, although one of each of the organs named is adequate for normal life, there are two ovaries, two eyes, two testes, two kidneys and two suprarenal glands; although only one spermatozoon is necessary to fertilize an ovum, large numbers ordinarily make the attempt. Gastric secretions, bile and intestinal secretions are produced in superabundance. It is timely to consider that blood may normally clot in blood vessels *too well* to serve the best interests of the health of man. The protective device provided by nature is actually harmful as well as protective. Nature has provided not wisely but too well. This conception requires acceptance of two verities: men and animals may live normally (in the absence of injury) if coagulation of the blood is substantially impaired, and thrombosis of blood vessels occurs less readily when blood clots less well than it normally does.

It is true that the importance of diseases of blood vessels would be greatly lessened if vascular disease did not provoke thrombosis and if the blood would not clot inside living blood vessels. Phlebitis would be a very benign disease if it did not cause venous thrombosis. Arteriosclerosis would have lesser importance if it did not cause coronary and cerebral thrombosis. The two chronic occlusive arterial diseases of the extremities, thrombo-arteriosclerosis obliterans and thrombo-angiitis obliterans, would not impair, greatly, the arterial circulation to the extremities if thrombosis were not a part of them. The curse of cardiac irregularities, coronary thrombosis and congestive heart failure would be substantially smaller if mural thrombosis and embolism were not associated with them. There would be no pulmonary embolism if blood would not clot inside blood vessels; the gangrene of trench foot and immersion foot would be avoided in many instances. These observations emphasize that the health of man would be greatly improved if intravascular thrombosis did not occur. The use of anticoagulants is a step in the direction of achievement of preventing intravascular thrombosis.

Currently, there are two preparations, used clinically, which impair the coagulation of the blood when administered to man: heparin and dicumarol. The disadvantages of the use of the former are its high cost and the need for parenteral administration;* the disadvantages of the use of the latter are the need for repeated determination of its effect by a laboratory procedure, the delay in effect after administration and the continuance of effect after administration has been stopped. The disadvantage of the use of both anticoagulants is that hemorrhage may result from the use of them. Every physician who uses anticoagulants must steer a course between the Scylla of too little and the Charybdis of too much.

THE SIMULTANEOUS USE OF HEPARIN AND DICUMAROL

Because the effect of dicumarol is delayed after oral administration, heparin must be used when a quick effect on coagulation of the blood is

* The amount of heparin required to permit the intravenous injection of 50 mg. every four hours currently costs about \$9 a day. Enough dicumarol to produce the desired effects on the blood costs only a few cents each day.

desired. Heparin is effective within a few minutes after administration but dicumarol may not be effective for twenty-four to forty-eight hours. The usual program when a quick effect is needed in the treatment of adults with anticoagulants is to inject 50 mg. of heparin intravenously and to administer 300 mg. of dicumarol by mouth. Treatment with dicumarol is continued as indicated in the following paragraph, and heparin in the amount of 50 mg. is injected intravenously every four hours, until studies of the prothrombin indicate reduction to a satisfactory value (20 per cent). During treatment with heparin, blood should be drawn for determination of the value for prothrombin about three hours after the last intravenous injection of heparin. Although in theory heparin should be administered by continuous intravenous injection, the intermittent injection of it produces satisfactory results in clinical use.

THE DOSAGE OF DICUMAROL

It cannot be too strongly emphasized that the administration of dicumarol must be based on the value for prothrombin in the blood. Any other program may lead to disaster from hemorrhage or to inadequate control of coagulation. Identical amounts may produce widely dissimilar effects on prothrombin when administered to different persons. Indeed, the prothrombin of the blood of the same person may be affected dissimilarly by identical amounts of dicumarol given on different occasions. An indispensable factor in treatment with dicumarol is the availability of an experienced and absolutely reliable laboratory service. In our experience at the Mayo Clinic the Quick method of calculating the value for prothrombin has been found to be entirely reliable. With this method normal values for prothrombin give a prothrombin time of 19 to 21 seconds. A prothrombin time of 27 seconds indicates that the value for prothrombin in the blood is 80 per cent of normal, 35 seconds indicates that the value is 20 per cent of normal and 60 seconds indicates that the value is 10 per cent of normal. I make a plea for discontinuation of the practice of reporting "prothrombin time." Since thromboplastins vary in potency, the time reported by one group of investigators could not be interpreted by other investigators who use another thromboplastin. In the interest of uniformity every publication should report the prothrombin, not in seconds but in "percentage of normal." At the very least, every publication should contain the prothrombin time for three critical values for prothrombin, namely, 80 per cent, 20 per cent and 10 per cent of normal.

Attention must be given to the thromboplastic substances used, for they vary in potency and identical prothrombin times for two lots of thromboplastin may indicate entirely different values for prothrombin (percentage of normal). When the Quick test for prothrombin time is performed repeatedly during treatment with dicumarol, either each batch of thromboplastin must be proved to have the same potency as the former, or a new dilution curve should be plotted for each new batch. The problem has been simplified by the observation that the critical figures in treatment with dicumarol are those representing 10 per cent, 20 per cent and 80 per cent of normal for prothrombin. One may administer dicumarol adequately knowing only these figures, for clinical experience has indicated that intravascular thrombosis rarely occurs when the value for prothrombin in the

blood is less than 30 per cent of normal and that bleeding rarely occurs when the value for prothrombin is 10 per cent of normal or more.

Three hundred milligrams of dicumarol are given on the first day and on each subsequent day of therapy the value for prothrombin is determined and reported. If the value is more than 20 per cent of normal, 200 mg. are given; if it is less than 20 per cent, none is given. There are minor exceptions to this program. If the patient's blood is sensitive to the effect of dicumarol, only 100 mg. may be given instead of 200 mg. If the patient's blood is insensitive to the effect of dicumarol, 300 mg. may be given instead of 200 mg. If the value for prothrombin is decreasing rapidly but is more than 20 per cent, no dicumarol is given; if it is rising rapidly but has not yet quite reached 20 per cent, the drug is given on that day. Ordinarily treatment with dicumarol, of patients who have venous thrombosis, is continued until the patient has been ambulatory for about one week. The effect of dicumarol ordinarily continues for a few days after discontinuation of treatment. It is doubtful that protection is afforded against intravascular thrombosis when the prothrombin value for the blood is between 30 per cent (approximation) and normal.

CONTROL OF EXCESSIVE PROTHROMBIN DEFICIENCY AND INDUCED HEMORRHAGE

It was originally believed that vitamin K was ineffective in correcting prothrombin deficiency induced by dicumarol. It is now known that the amounts of vitamin K which were used were entirely inadequate. It is of some historical interest that Butt and I gave 30 mg. of synthetic vitamin K intravenously to the first patient to whom we gave dicumarol. There was a prompt increase in the value for prothrombin in the blood. We misinterpreted this as a natural event, not resulting from the intravenous injection of vitamin K. We did not recognize our error until considerable time after others had shown that large amounts of vitamin K would correct the hypoprothrombinemia induced by dicumarol. In studies by Barker and associates it was shown that 64 mg. of menadione bisulfite, injected intravenously, corrected excessive prothrombin deficiencies in thirty-five of thirty-seven patients, and bleeding ceased. Transfusion of 500 c.c. of blood is also effective; it may need to be given as required until bleeding stops and the anemia is corrected. The appearance of excessive prothrombin deficiency is a signal to discontinue dicumarol therapy temporarily, and to resume with smaller doses. If an emergency operation must be performed on a patient who is receiving heparin, discontinuation of therapy for two or three hours will permit the blood to return to a normal state of coagulability. If an emergency operation must be performed on a patient receiving dicumarol, large amounts of vitamin K and transfusions may be given to cause return of the prothrombin value toward normal.

VARIATIONS IN PROTHROMBIN AND ANTITHROMBIN FOLLOWING THE ADMINISTRATION OF DICUMAROL*

MARGARET HUHN, NELSON W BARKER AND FRANK D MANN

By both the two-stage method and the Quick method, a marked decrease in prothrombin level was observed after the administration of dicumarol.

Early in the course of the dicumarol therapy, the levels of prothrombin as established by the Quick test were always less than, often less than half, those obtained with the two-stage method. As administration of dicumarol was discontinued, there was a tendency for this difference to disappear and finally for the one-stage method to give slightly higher values than the two-stage method. This difference in results obtained with the two methods would seem to indicate a decreased rate of conversion of prothrombin to thrombin.

In all instances there was an increase in the antithrombin activity of the serum after the administration of dicumarol.

OBSERVATIONS ON THE CONVERSION OF PROTHROMBIN TO THROMBIN†

FRANK D MANN, MARGARET HUHN AND THOMAS B MAGATH

Fresh plasma, serum and platelet extracts contain a material which potentiates the action of tissue thromboplastin on stored plasma. Platelet extract apparently contains a greater degree of this activity than plasma or serum and potentiates the action of tissue thromboplastin on fresh plasma. This factor favoring prothrombin conversion apparently is present in the circulating blood

RESPONSE OF PERSONS WITH AND WITHOUT INTRAVASCULAR THROMBOSIS TO A HEPARIN TOLERANCE TEST‡

ALBERT B. HAGEDORN AND NELSON W BARKER

The coagulation time of 1 c.c of venous blood placed in a 10 by 75 mm. Wassermann-type glass tube and inverted every thirty seconds has been obtained on fifty control subjects and seventy patients before and after the intravenous injection of 25 mg of heparin in 2.5 c.c. of liquid.

The results of the determinations of coagulation time on samples of

* Abstract of paper published in full in the *American Journal of Clinical Pathology*, 17:712-718 (Sept.) 1947.

† Abstract of paper published in full in the *Proceedings of the Society for Experimental Biology and Medicine*, 66:33-35 (Oct.) 1947

‡ Abstract of paper published in full in the *American Heart Journal*, 37:603-610 (Apr.) 1948

venous blood withdrawn at ten minute intervals for variable periods indicated that the maximal response to the intravenous injection of heparin occurred ten minutes after injection.

Of the individuals without evidence of intravascular thrombosis, including the control subjects, 5 per cent were hyperreactors; 88 per cent, normal reactors; 7 per cent hyporeactors, and none were nonreactors.

Of the individuals with evidence of intravascular thrombosis (categories 1 to 4), none were hyperreactors, 31 per cent were normal reactors, 30 per cent were hyporeactors and 39 per cent were nonreactors.

NEUTRALIZATION OF HEPARIN WITH PROTAMINE (SALMINE)*

THOMAS W. PARKIN AND WALTER F. KVALE

Hemorrhage due to a prolonged blood coagulation time resulting from the administration of heparin can be controlled only by discontinuing the administration of heparin and by giving blood transfusions. The effects of neither of these procedures may be sufficiently prompt to prevent the hemorrhage reaching serious proportions.

Certain protamines are known to neutralize heparin *in vitro* and in animals. Protamines also appear to have certain toxic effects when given to different species of animals. The assumption appears in the literature that on the basis of animal studies protamines cannot be administered safely to human beings. On the contrary, in 1938, Jorpes reported from Sweden that the protamine, clopeine, can be injected intravenously in man to neutralize heparin. In view of the conflicting reports in the literature further work seemed necessary.

The purpose of this investigation was to determine (1) by work on animals the toxicity of the protamine, salmine, (2) if salmine can be administered safely to man and (3) the dosage of salmine required to neutralize the anticoagulant effect of a standard dose of heparin in man.

In vitro studies demonstrated that 1.5 mg. of salmine neutralized 1.0 mg. of heparin, thus showing that there is quantitative neutralization. The lethal dose of salmine in the guinea pig was 6.0 mg. per 100 gm. of body weight. Salmine injected intravenously in doses of 90.0 mg. per kilogram in the unanesthetized rabbit and 2.0 mg. per kilogram in the unanesthetized dog produced no reactions. The intravenous injection of salmine in doses of 10.0 mg. per kilogram in the anesthetized rabbit and 2.0 mg. per kilogram in the anesthetized dog produced transient drops in arterial blood pressure. No evidence of anaphylaxis was observed.

Intravenous injections of salmine neutralized heparin which was injected intravenously in dogs. In the dog, elevated coagulation times resulting from the intramuscular injection of heparin in the Pitkin menstruum were temporarily returned to normal levels by single intravenous injections of salmine.

* Abstract, published in the Proceedings of the Central Society for Clinical Research. *10.5*, 1947; *Journal of Laboratory and Clinical Medicine*. 32:1396 (Nov.) 1947.

The anticoagulant effect of intravenous injections of heparin in man was studied by determining coagulation times at fifteen to thirty minute intervals for a period of three hours. Coagulation times were determined by the Lee-White method with a thermostatically controlled water bath at 37° C. It was found that coagulation times were elevated four times the normal (four minutes) one hour after injection and then they gradually returned to preheparin levels in three hours. With this to serve as a control, 50 mg. of heparin was injected intravenously in ten persons and fifteen minutes later salmine was injected intravenously in doses ranging from 15 to 50 mg. In the patients receiving 40 to 50 mg. of salmine, the elevated coagulation times were returned to normal levels within five minutes.

No toxic reactions were noted in any patient during or after the injections of salmine. It is concluded that the intravenous injection of 40 to 50 mg. of salmine promptly neutralizes the anticoagulant effect of 50 mg. of heparin and that such doses of salmine, when given slowly, produce no reactions.

HYPOPROTHROMBINEMIA: EFFECT OF TRANSFUSIONS OF BLOOD FORTIFIED BY ADMINISTRATION OF VITAMIN K TO DONORS*

HUGH R. BUTT, THOMAS B. MAGATH AND THOMAS H. SELDON

Data are presented on three patients with severe hepatic damage accompanied by deficiency of prothrombin in the circulating blood. Again, it has been confirmed that the deficiency of prothrombin which frequently occurs in this type of condition usually cannot be corrected by administration of vitamin K or of whole blood. It also has been shown that the administration of so-called fortified blood is not effective in altering the prothrombin level in these patients. Not only was fortified blood of no value in correcting prothrombin deficiency in these patients with severe intrahepatic disease but, likewise, it was ineffectual in the correction of the deficiency of prothrombin in external biliary obstruction in spite of the fact that the latter condition was quickly remedied by the administration of vitamin K alone.

THE MEDICAL USE OF RADIOACTIVE ISOTOPES I. RADIOACTIVE ISOTOPES IN HEMATOLOGIC DISTURBANCES AND NEOPLASMS†

BYRON E. HALL AND CHARLES H. WATKINS

On the basis of present evidence, radiophosphorus therapy provides an effective means for the control of polycythemia vera. Remission, often of long duration, can be induced in a high proportion of cases. The chief ad-

* Abstract of paper published in full in the *Archives of Internal Medicine*, 81:131-136 (Feb) 1949.

† Abstract of paper published in full in the *American Journal of the Medical Sciences* 213 621-628 (May) 1947.

vantages of this form of treatment appear to be the ease of administration, the absence of radiation sickness and symptoms of toxicity and the simplicity with which the dose can be controlled. The principal disadvantages are the cost of the material and the fact that the bone marrow may be injured seriously in the case of overdosage or an unusual sensitivity of the marrow to therapeutic doses. Moreover, the possibility that radiophosphorus may cause terminal acute leukemia must be borne in mind. In chronic leukemia, radiophosphorus induces remission similar to that produced with roentgen rays, but therapy with this isotope apparently has no particular advantage over the latter form of treatment and requires a longer period to bring about the desired result. In multiple myeloma, radiophosphorus relieves pain in bones in a significant proportion of cases, but does not inhibit the systemic progression of the disease. In the lymphomas, radiophosphorus therapy appears to be less effective than roentgen-ray treatment, and in acute leukemia, metastatic tumors, mycosis fungoides and xanthomatosis, the isotope is ineffective as a therapeutic agent.

TREATMENT OF DISEASES OF THE HEMATOPOIETIC SYSTEM WITH RADIOPHOSPHORUS*†

BYRON E. HALL

This study is based on an analysis of the results obtained with radiophosphorus in the treatment of 124 cases of polycythemia vera, thirty-three cases of leukemia, twenty-five cases of multiple myelomas, and two cases of Hodgkin's disease with extensive involvement of the bone marrow.

The intravenous route of administration of the isotope was employed in all cases. In polycythemia vera, the initial dose of radiophosphorus varied from 3 to 7 mc.; the size of the dose was calculated on the basis of body weight, age of the patient and clinical severity of the disease. In cases in which remission was not induced by the initial injection of the isotope, subsequent injections were given at intervals of six weeks to three months until the desired result was obtained. In leukemia, myeloma, and Hodgkin's disease, either the fractional or the fractional saturation methods of administering radiophosphorus, as advocated by Low-Beer, Lawrence and Stone, was employed. An initial injection of from 1 to 2 mc. of radiophosphorus usually was given. This was followed by the administration of smaller quantities of the isotope twice weekly until the desired clinical and hematologic effect was noted.

In polycythemia vera, satisfactory remissions accompanied by symptomatic improvement were observed in 85 per cent of the patients treated

* Read at the Fourth International Cancer Research Congress, St. Louis, Missouri, September 2 to 7, 1917.

† For a detailed report on this subject, the reader is referred to an article by the author, "Therapeutic use of radiophosphorus in polycythemia vera, leukemia and allied diseases," in a symposium on the use of isotopes in biology and medicine. University of Wisconsin Press (in press.)

with the isotope, and partial remissions were noted in 8 per cent. In 7 per cent, no improvement occurred, but in three fourths of the last group treatment was inadequate largely because of lack of co-operation on the part of the patient. The remissions lasted from six months to two years after the first course of treatment in most cases. Remissions lasting three years were noted in two cases, four years in one case, and five years in one case. Treatment with the isotope resulted in the development of leukopenia in 29 per cent of the cases, thrombocytopenia in 22 per cent and anemia in 16 per cent. In all except one case, recovery was complete in the course of a few weeks. In one instance, severe anemia associated with marked hypoplasia of the bone marrow was encountered after the administration of a therapeutic dose of radiophosphorus and it was nine months before the peripheral blood picture returned to normal. The incidence of leukopenia and anemia in our series of cases is somewhat lower, and the incidence of thrombocytopenia somewhat higher than that reported by Reinhard and associates.

Six deaths have occurred among the 124 patients who had polycythemia vera. Four of these resulted from the development of a terminal acute fulminating leukemia, one from cerebrovascular accident (no necropsy) and one from congestive heart failure. It is of interest that different types of acute leukemia were observed in each of the four cases in which death was due to acute leukemia. These were leukopenic myelogenous leukemia, monocytic leukemia of Naegeli type, lymphocytic leukemia and pancytopenia. In the last, the erythrocytic cell line was involved primarily by the leukemic process, although the granulocytic cell strain and the reticulo-endothelium were involved also. In all four patients, a leukemoid reaction of myeloid type was present prior to the administration of radiophosphorus. Since the development of acute leukemia as a terminal event in polycythemia vera has been exceedingly rare among patients treated by means other than the administration of radiophosphorus, the possibility of radiation leukemia resulting from the introduction of the isotope into the human being has been raised. Observation over a prolonged period, however, will be necessary before this question can be settled.

A diminished incidence of thrombophlebitis and thrombosis was noted during periods of remission in cases of polycythemia. A history of episodes of thrombophlebitis or thrombotic phenomena was obtained from 27.4 per cent of the patients before treatment with radiophosphorus. Following treatment, 2.4 per cent suffered from attacks of thrombophlebitis, but the disease of all these patients was controlled inadequately.

In twenty cases of chronic myelogenous leukemia and in six cases of chronic lymphatic leukemia, remissions were induced with radiophosphorus in a manner similar to the induction of remissions by means of roentgen irradiation. All of the patients who had chronic lymphatic leukemia are living at the present time; ten of the patients who had chronic myelogenous leukemia are dead. Six of the latter group died from a terminal acute leukemia; the incidence of an acute terminal phase presumably was higher than it is among patients who have chronic myelogenous leukemia treated by means of roentgen rays.

Radiophosphorus, as the sole therapeutic agent, was ineffective in four cases of acute leukemia, two cases of Hodgkin's disease, and twelve cases of

myeloma. In twelve additional cases of myeloma, intensive roentgen irradiation was administered after treatment with radiophosphorus. In general, these results were poor also, although in one case local regression of multiple tumors followed by bone repair occurred. It is of interest, however, that treatment of plasma-cell leukemia with radiophosphorus resulted in a remission lasting eighteen months in one case. In the light of this observation, it is felt that isotopes should be employed in additional cases of plasma-cell leukemia in order to permit evaluation of the therapeutic effectiveness of radiophosphorus in this disease.

THE USE OF URETHANE (ETHYL CARBAMATE) IN THE TREATMENT OF LEUKEMIA: A PRELIMINARY REPORT*

CHARLES H. WATKINS, TALBERT COOPER AND HERBERT Z. GIFFIN

Our experience would indicate that urethane can be expected to produce a temporary hematologic remission in cases of chronic myelogenous leukemia. This remission is similar, in superficial characteristics, to that observed after irradiation therapy. There is, at the present time, no indication that urethane offers more than other agents which are used palliatively in this disease. However, by virtue of its convenience of administration and the possible advantage of controlled, continuous action, urethane may be found preferable to other methods of treatment in use at the present time.

We have had insufficient experience with the use of urethane in the treatment of chronic lymphatic leukemia to warrant an opinion as to its efficacy. However, the reported experiences of Paterson and co-workers would seem to justify continued use of the substance in such cases.

While, like irradiation therapy, urethane may produce a rapid decrease in the number of immature leukocytes circulating in the blood in some cases of acute myelogenous and lymphatic leukemia, there is no evidence to suggest that the usual course of these conditions has been beneficially influenced.

Despite the absence of serious toxic effects encountered in this series to date, the potential production of *aplastic anemia* and other complications by this substance must be kept in mind.

* Abstract of paper published in full in *Blood*. (In press.)

EXPERIENCE WITH PTEROYLGLUTAMIC (SYNTHETIC FOLIC) ACID IN THE TREATMENT OF PERNICIOUS ANEMIA*

BYRON E. HALL AND CHARLES H. WATKINS

Fourteen patients who had Addisonian pernicious anemia in relapse were treated with pteroylglutamic (synthetic folic) acid over periods from twenty-four days to nine months. The most striking effect of this form of therapy was observed in the bone marrow, erythropoiesis rapidly changing from a megaloblastic to a normoblastic type. However, considerable variation in the rate of erythrocytic regeneration was encountered, and in certain instances normal blood values were not obtained after several months of treatment with pteroylglutamic acid in doses generally thought to be relatively large.

Symptomatic improvement also was variable. Treatment resulted in abatement of glossitis and peripheral neuropathy in most cases, but recurrence was common among persons maintained solely on this form of therapy for a period of months. Moreover, peripheral neuropathy and subacute combined degeneration of the spinal cord developed as new manifestations in a significant proportion of cases two to five months after treatment was begun. In the light of these observations, it is obvious that pteroylglutamic acid does not prevent the occurrence of degenerative disease of the peripheral nerves and spinal cord in pernicious anemia, and that the use of this form of therapy as a substitute for extracts of liver or gastric mucosa subjects patients to the hazards of progression or development of the neural manifestations of the disease. On the other hand, pteroylglutamic acid has been found to be an effective therapeutic agent in certain macrocytic anemias related to pernicious anemia, a subject not considered in the present paper.

PRIMARY NONFAMILIAL HEMOLYTIC ANEMIA†

J. M. STICKNEY AND FRANK J. HECK

Although patients with hemolytic anemia are not numerous, they continue to be a problem of special interest and great difficulty. In the majority of cases the disease is of the familial or congenital type. The commonly accepted criteria for the diagnosis of congenital hemolytic anemia include the presence of a microspherocytic blood picture with an increase in signs of regenerative activity, increased fragility of the erythrocytes in varying concentrations of hypotonic saline solution, splenomegaly, an elevated value for indirect serum bilirubin with an increased excretion of fecal urobilinogen, and a history of anemia, icterus, splenomegaly or increased fragility of erythrocytes in other members of the patient's family.

* Abstract of paper published in full in the *Journal of Laboratory and Clinical Medicine*, 32:622-634 (June) 1947.

† Abridgment of paper published in full in *Blood*, 3: 431-437 (Apr) 1948

In the differential diagnosis of the different types of hemolytic anemia, the question not infrequently arises as to whether an individual instance of the disease should be regarded as belonging to the congenital or familial type or to the acquired type. As Watson pointed out, there has been a tendency to regard all instances of "primary hemolytic jaundice as of familial or congenital type." There are, however, no clear-cut criteria to which all writers on the subject agree. In some cases in which the family history is negative but other criteria are present, the disease is classified as acquired. It must be admitted that a negative family history is not a definite indication that the disease is of the acquired type since actual investigation of close relatives may reveal such changes as increased fragility of the erythrocytes in the absence of other findings.

In the years 1942 through 1946, at the Mayo Clinic, splenectomy was performed in twenty-two cases of hemolytic anemia in which no positive family history could be obtained. These twenty-two cases are the object of our special interest.* As far as could be determined, the hemolytic syndrome in these cases was not secondary to any toxic, infectious or poisonous agent and was not symptomatic and part of a primary disease such as lymphoblastoma, leukemia or hepatic cirrhosis.

We have divided these cases into two groups which happen to be equal in number. In the first group, either microspherocytosis or increased fragility of the erythrocytes or both were found. In the second group, such evidence was not present. The groups are summarized in tables I and 2.

All of our cases were examples of primary nonfamilial hemolytic anemia so far as we could determine. Microspherocytosis was not present in half of these cases but with one exception (case 13) we could not classify them as cases of macrocytic anemia. There was a considerable number of macrocytes in some of the smears but many of them were regenerative or polychromatophilic erythrocytes.

Agglutinins and hemolysins may be etiologic factors in a hemolytic syndrome. In two of our cases (cases 14 and 22) iso-agglutinins of an abnormal type were present. In each instance, the patient's serum agglutinated his own erythrocytes. In another case (case 4), an Rh negative patient had a high Rh antibody titer due to previous transfusions of Rh positive blood. Although the blood picture was microspherocytic, it is possible that this antibody titer may have been the cause of the hemolytic anemia. In any event, improvement did not occur until splenectomy was done. At the present time, a more intensive search for irregular agglutinins and hemolysins is being carried out in certain cases of hemolytic anemia.

Several authors have emphasized the dangers of severe hemolytic reactions following blood transfusion in hemolytic anemia. In one of our cases (case 10), death was probably due to a hemolytic transfusion reaction after operation. We have not noted any severe exacerbation of the hemolytic process in the other cases but we have been impressed with the failure of transfusion to benefit the patient, especially before splenectomy.

We have found it difficult to correlate the degree of anemia with the severity of the jaundice. In one case (case 4) as long as the patient was

* In the years 1942 through 1946, a diagnosis of congenital hemolytic icterus was made in 113 cases at the Mayo Clinic. Splenectomy was performed in approximately ninety of these cases.

TABLE 1
HEMOLYTIC ANEMIA WITH SIGNIFICANT MICROSPIRUCYTOSIS

Case	Age, years, sex	Before splenectomy					After splenectomy			
		Hemoglobin, gm per 100 c.c.	Erythrocytes		Reticulocytes, per cent	Gallstones	Time followed, mos.	Hemoglobin, per 100 c.c.	Erythrocytes, no per cu. mm.	Result
			No. per cu mm	Fragility, per cent*						
1	26, F	3.9	1,390,000	0.46-0.59	25	0	13		4,100,000	Improvement
2	30, F	0.0	1,590,000	0.59-0.59	62	0	30		4,000,000	Excellent
3	33, F	11.0	9,140,000	0.41-0.52	18	+	12	8.9 gm	2,740,000	Poor†
4	39, F	8.4	2,320,000	0.50-0.59	51	+	1	10.4 gm	4,520,000	Improvement
5	39, F	8.9	2,710,000	0.40-0.52	32	0	9	81%	2,537,000	Excellent
6	54, F	8.4	2,900,000	0.40-0.56	24	+	26	88%		Excellent
7	59, F	6.5	3,850,000	0.48-0.56	3	0	12	12.5 gm	3,850,000	Excellent
8	60, M	6.8	2,000,000	0.50-0.54	37	0	24	90%	5,000,000	Excellent
9	61, F	4.9	1,640,000	0.46-0.49	40	0	4	13.6 gm.	3,760,000	Excellent†
10	65, F	0.0	1,520,000	0.50-0.56		0				Died 8th postoperative day Transfusion reaction
11	74, M	4.3	1,150,000	0.50-0.56	27	0	21	60%	2,800,000	Fair

* In hypotonic solution of sodium chloride

† Reported in detail in text of complete paper

TABLE 2
HYPOTENSIVE ANEMIA WITHOUT SIGNIFICANT MICROCYTHROMATOSIS

Case	Age, years, sex	Before splenectomy					After splenectomy				
		Hemoglobin, gm. per 100 c.c.	Erythrocytes		Reticu- locytes, per cent	Gallstones	Time followed, mos.	Hemoglobin, per 100 c.c.	Erythrocytes, no. per cu mm.	Result	
			No. per cu mm.	Fragility, per cent*							
12	4, F	8.1	2,770,000	0.40-0.59	13	0	24	5.8 gm.	2,580,000	Poor. Explored for accessory spleen	
13	15, M	10.3	3,370,000	0.44-0.50	10	+	24	10.6 gm.	2,080,000	Poor†	
14	19, F	4.5	800,000	0.46-0.56	40	0	12		3,750,000	Excellent	
15	21, F	6.8	2,530,000	0.44-0.51	32	0	23	78%	4,120,000	Excellent†	
16	24, F	11.9	4,100,000	0.44-0.52	5	+	†	15.8 gm.		Improvement.	
17	35, M	6.5	2,320,000	0.44-0.52	17		40	14.8 gm.		Excellent‡	
18	54, F	11.6	3,350,000	0.42-0.50	12	+	13	78%	3,400,000	Fair. One episode of jaundice.	
19	40, F	4.9	1,560,000	0.44-0.50	50	0	4	11.0 gm.		Died of intestinal obstruction.	
20	46, F	8.1	3,850,000	0.48-0.53	5	+	1	11.05 gm.	4,920,000	Unknown	
21	54, F	5.5	1,310,000	0.44-0.50	50	+	12	12.9 gm.	4,050,000	Excellent	
22	59, F	4.7	1,520,000	0.44-0.52	51	0	4	10.2 gm.	4,000,000	Died of serum hepatitis	

* In hypotonic solution of sodium chloride.

† Reported in detail in text of complete paper.

‡ Course following splenectomy reported through courtesy of Dr. C. J. Watson.

severely jaundiced the anemia was relatively mild. When the severity of the jaundice decreased, the concentration of hemoglobin decreased rapidly. This inverse relationship has been noted by Watson and Fowler.

In several of our cases bone marrow was examined. A definite hyperplasia of the normoblastic cells was seen in each instance. No megaloblasts were found.

Although not common, leukopenia and thrombocytopenia may accompany the anemia. Doan and Wright have recently reported this phenomenon as a panhematopenia. In case 14, the number of leukocytes ranged from 3,100 to 5,000 and the number of thrombocytes from 65,000 to 75,000 per cubic millimeter before splenectomy. Both were normal or increased in number after operation.

In a case not included in this series splenectomy was performed for what appeared to be a primary hemolytic anemia. The blood picture was subsequently that of chronic myelogenous leukemia. At the time of the original examination, there was not as much myeloid immaturity as there was in the blood of many of the patients in the present series. The sternal marrow was hyperplastic and could not be distinguished from nonleukemic hyperplastic marrow.

Splenectomy may be of definite benefit in symptomatic hemolytic anemia when the progress of the primary disease is not rapid. Recently, a woman who was sixty-six years of age came to the clinic because of weakness of six months' duration. The hemoglobin value was 8.3 gm; the erythrocyte count was 2,250,000 with 15 per cent reticulocytes. A spleen which weighed 1,125 gm. was removed and a diagnosis of follicular lymphoblastoma was made. There were no enlarged lymph nodes. One year later, the patient, who had regained her good health, returned because of enlarged axillary and inguinal lymph nodes. The hemoglobin value then was 11.7 gm. and the erythrocyte count was 4,150,000. Biopsy of a lymph node confirmed the previous diagnosis and for the first time roentgen therapy was started. The splenectomy had relieved the weakness and anemia.

THE DIAGNOSIS OF MULTIPLE MYELOMA*

EDWIN D. BAYRD

CLINICAL FEATURES OF THE DISEASE

Multiple myeloma is virtually undiagnosable from the history alone and little more may be expected from the physical examination.

Pain, the most prominent symptom of all, will have occurred in about 85 per cent of cases by the time that the clinician first sees the patient. It is usually in the thorax or back, often is precipitated by trauma, is eased by rest and worsened by exertion. It is variable though progressive and often excruciating.

Anemia is common to more than half of these patients at the level of

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clinical appreciation, and will be encountered as a rule after liver and iron therapy have failed to effect any improvement. It has no specific characteristics, may be macrocytic, microcytic or normocytic, and is of help only in so far as it spurs one to find its cause.

Pathologic fracture and formation of tumors are suggestive when present. In our experience, pathologic fracture and formation of tumors (when clinically evident) have occurred in somewhat less than a fifth of the cases. Because of the nature of this disease both of these phenomena should be sought for in that portion of the bone where erythropoiesis is most active.

Paraplegia and root pain, resulting from collapse of the vertebral bodies, will be encountered in approximately a seventh of patients who have multiple myeloma.

Occasionally a patient will appear stating that his physician found large amounts of albumin in his urine on a routine examination, and that he was felt to be suffering from "Bright's disease." Examination will show persistently high grades of albuminuria with or without casts, cellular elements and azotemia, but usually without hypertension, hypoproteinemia or edema. Further investigations will, in most instances, yield a telltale sign of the real cause of the disturbance.

In a small but important number of patients, an abnormal tendency to bleeding (such as epistaxis) will be the most distressing, or only, symptom. This then must not be considered as a differential diagnostic point from the leukemias. Since the serum proteins are almost always elevated when bleeding occurs, confirmation will usually be forthcoming from this source.

ROENTGENOGRAPHIC AND LABORATORY FINDINGS

Bence Jones proteinuria, the handmaiden of multiple myeloma for years, may be expected to be observed in approximately half of all cases seen at the time the diagnosis is first made. As is well known, this is not a pathognomonic finding, but when it is present, the chances are probably greater than 95 per cent that it is due to multiple myeloma.

Roentgenographic evidence of multiple osteolytic bone lesions was obtained in approximately 78 per cent of the cases at the Mayo Clinic. This is valuable evidence, which, if properly followed up, should lead to the diagnosis as often as it is encountered. In 12 per cent of the cases at the clinic no gross defects of the skeleton were noted. In the remainder of cases, varying degrees of osteoporosis with ballooning of the intervertebral disks was seen, with and without compression of the vertebrae. The significance of this and of a high erythrocytic sedimentation rate has been emphasized.

Serum protein will be found to be elevated above 8 gm. per 100 c.c. of serum in approximately three fourths of all cases. Of this the main component is always globulin.

A corollary to hyperglobulinemia is increased formation of rouleaux, as may be seen in smears of the peripheral blood, and autohemagglutination, which may first be observed as the patient is cross-matched or grouped for a transfusion, or when an erythrocyte count is done. A stubborn, refractory anemia will frequently be found, as previously noted.

Leukemoid reactions are fairly common, and it may be anticipated that stem cells will be seen in the peripheral blood in about a fifth of the cases studied.

When destruction of bone is rapid the concentration of calcium in the serum may be elevated and may cause confusion with hyperparathyroidism. Excretion of calcium in the urine will likewise be increased. Moreover, the concentration of phosphorus in the serum may be coincidentally low, while phosphatase values are elevated. This obviously makes for a difficult diagnostic problem and only with extreme care will surgical intervention be avoided. This is unusual, however. More frequently the concentration of phosphorus will be found to be elevated also and usually the phosphatase values will be normal. Hypercalcemia has occurred in 20 per cent of cases in our experience.

Myeloma cells will fairly frequently be seen in smears of the peripheral blood if a careful search is made under low power of the microscope. Less frequently they will occur in large numbers in the peripheral blood and give rise to a diagnosis of plasma-cell leukemia.

THE BONE MARROW

Biopsy is usually a satisfactory method of obtaining material, but this may fail to give the desired information. By far the easiest and probably the most consistently accurate diagnostic method is that of sternal aspiration. Briefly, the plasma myeloma cells, on smears of the sternal marrow treated with the usual Romanowsky stain, are characterized by a deep basophilic, abundant cytoplasm of an uneven, "granular" character. This cytoplasm is often vacuolated and occasionally contains Russell bodies. Free, round cytoplasmic bodies may be seen in more than 90 per cent of marrow studies. The nucleus may or may not contain a large, clear single nucleolus (rarely multiple nucleoli) and be eccentrically placed. It may be markedly differentiated or may be pleomorphic and anaplastic. Hypernucleation is common, probably can be noted in every case, and occasionally will approach a frequency of 10 per cent of plasma myeloma cells present. Mitosis is not common, but may be numerous in those cases in which it is seen.

POTASSIUM INTOXICATION IN UREMIA*

NORMAN M. KEITH AND HOWARD B. BURCHELL

Further observations have been made concerning the value for serum potassium among patients who have severe renal insufficiency. Although hyperpotassemia is rare in uremia, thirteen patients have now been observed who had values for serum potassium in excess of 7.5 milliequivalents. The highest value recorded has been 10.5 milliequivalents. The factors which control the serum level of this cation are but poorly understood, and the major interest, at present, is the belief that hyperpotassemia may be the immediate cause of the death of some patients through the mechanism of cardiac arrest. This belief is based chiefly on the electrocardiographic changes which develop in association with progressive increments in serum

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potassium. These changes, beginning as a peaking of the T wave with narrowing of its base, and with higher values for potassium, marked widening of the QRS complex and absence of P waves, have become a stereotyped pattern, sufficient to indicate the diagnosis of hyperpotassemia. Potassium salts have been used as diuretic agents in chronic nephritis, and were given to two of our patients with toxic effects. Two other patients received test doses of 5 gm. of potassium bicarbonate; then the values for serum potassium and electrocardiograms were studied. No untoward clinical reaction resulted, but the values for serum obtained would indicate the potential danger of the use of potassium salts in severe renal insufficiency. Necropsy of ten of the thirteen patients was carried out, and the relatively normal myocardium found in the majority of the ten cases is to be contrasted with the striking electrocardiographic abnormality.

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SKIN AND SYPHILIS

XANTHOMATOSES*

PAUL A. O'LEARY AND HAMILTON MONTGOMERY

Disturbances of lipid metabolism usually are characterized by skin lesions and systemic manifestations which often are of a serious nature. It is difficult to make a satisfactory working classification of the lipid disturbances in view of our present inadequate knowledge of lipid metabolism. Multiple classifications have been given in the past. The grouping in this paper is a simplified one and deals essentially with lipid disturbances having cutaneous manifestations. The term "xanthoma," which means "yellow



Fig 56a—Xanthoma palpebrarum (xanthelasma). b. Xanthoma tuberosum (xanthic tumor of tendon sheath)

tumor," is frequently a misnomer because many of these patients do not have tumors; nonetheless, common usage warrants continued use of the term.

The most common type of cutaneous xanthoma is that known as *xanthoma palpebrarum* (xanthelasma). It occurs as small yellow to orange or orange-red colored papules and nodules or plaques involving the eyelids (fig. 56a). The majority of the lesions are located toward the inner canthi but, occasionally, the lesions are numerous and thick enough to interfere with vision. About 50 per cent of the patients who have xanthoma palpebrarum do not display any evidence of hyperlipemia or associated systemic disease, although the lesions of the eyelids may occur in association with other forms of xanthoma or may be the first manifestation of severe hyperlipemia associated with cardiovascular or hepatic disease.

Xanthoma tuberosum, the second most common form of xanthomatous disease, occurs at any age and is characterized by predominance of lesions on the extensor surfaces, especially the elbows, knees and tendon sheaths (fig. 56b). The lesions may be solitary or multiple, vary in size from a few

* From the Canadian Medical Association Journal. 57:445-452 (Nov.) 1947.

millimeters to several centimeters or more and display a variety of colors from yellow to reddish brown. Hyperlipemia with increase especially of cholesterol is found in association with xanthoma tuberosum. In almost half of these cases, there is evidence of cardiovascular disease, usually of coronary sclerosis with angina pectoris or of occlusive vascular disease of the extremities with *intermittent claudication* which appears often in the form of arteriosclerosis obliterans. In the *juvenile type of xanthoma tuberosum*, the mitral valve of the heart may be involved but vascular disease of the extremities is rare. A history of familial incidence of hyperlipemic states is usually elicited in patients who have the juvenile form of xanthoma tuberosum and a similar history is likewise common in the adult type of the disease.



Fig. 57a—Xanthoma tuberosum. Note variance in size of lesions occurring on elbow. b Xanthoma disseminatum of the axilla.

Müller has emphasized that hereditary heart disease due to xanthomatosis is fairly common, that the syndrome of cutaneous xanthomatosis, hypercholesterolemia and angina pectoris presents itself as a well-defined disease entity in the first, second, third and fourth generations and that it is a dominant hereditary disease. Polano and others have confirmed these findings. In studying a given family, one may find all combinations of the disease; thus, one member may have hyperlipemia only, another xanthelasma and a third the complete picture of cutaneous xanthoma, hyperlipemia and cardiovascular disease. It would also appear that angina pectoris and coronary disease develop at an earlier age in this group of patients than is true for angina pectoris in general, and cutaneous xanthoma may precede by several years the clinical manifestations of cardiovascular disease.

We observed a woman, twenty-eight years old, who had had extensive cutaneous lesions of xanthoma tuberosum for a period of six years (fig. 57a; contrast with xanthoma disseminatum, fig. 57b). Her blood plasma cholesterol was 667 mg. per 100 c.c. of plasma (normal 200 mg.) and her total lipids were 1,723 mg. per 100 c.c. of plasma (normal 550 mg.). The first general examination which she underwent included electrocardiography, special cardiovascular studies and roentgenograms of the legs for evidence of occlusive arterial disease, all of which were normal. When examined thirteen months later, no evidence of cardiovascular disease could be elicited. Nevertheless, she died at home a year later of angina pectoris, the symptoms having developed only a short time before death.

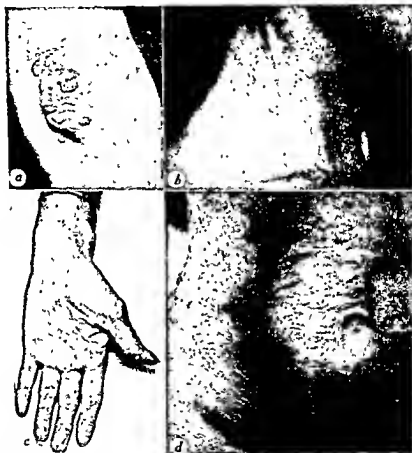


Fig. 58a.—Xanthoma tuberosum associated with xanthomatous biliary cirrhosis. b. Same case. Large plaque of diffuse xanthomatous infiltration. c. Xanthomatous biliary cirrhosis (Burger-Grütz type) showing involvement of creases of palm and fingers. d. Same case as c, showing diffuse xanthomatous plaques and involvement of laparotomy scar.

Xanthoma tuberosum in association with myxedema has been reported by Sweitzer and Winer. An increase of blood plasma cholesterol is of diagnostic value in cases of myxedema with or without evidence of cutaneous xanthoma.

Xanthoma tuberosum is associated with hepatic disease in about 15 per cent of the cases. It may occur in association with primary disease of the liver, so-called xanthomatous biliary cirrhosis (fig. 58a and b), or in associa-

tion with hepatic disease that is secondary to the obstruction of the common bile duct, especially as the result of postoperative stricture. In cases in which hepatic disease is primary, the prognosis is generally unfavorable while it is more favorable in the secondary types. Hepatic disease and hyperlipemia frequently precede the development of cutaneous lesions but not necessarily so. A special type of hepatic disease with hyperlipemia was described by Bürger and Grütz as hepatosplenomegaly with cutaneous and mucosal lipoidosis in which there is a marked and disproportionate increase of phosphatides rather than of cholesterol as occurs in other forms of hepatic xanthomatosis. Bürger and Grütz reported two cases, one without jaundice and one with jaundice. One of the characteristics of xanthoma in relation to hepatic disease is the tendency for the folds and creases of the palms and soles to be outlined by yellowish xanthomatous deposits (fig. 58c). Large superficial xanthomatous plaques may occur on the trunk and also in laparotomy scars (fig. 58d).



Fig. 59a —Xanthoma disseminatum. The histologic changes are similar to those of xanthoma tuberosum and xanthelasma. Note vacuolated foam or xanthoma cells, also typical Touton giant cells with circular arrangement of the nuclei ($\times 65$). b. Showing details of cells ($\times 150$).

Xanthoma diabeticorum does not differ materially in appearance or distribution from xanthoma tuberosum except that the lesions are likely to be more numerous and smaller in size. Thannhauser expressed the opinion that xanthoma diabeticorum is a secondary rather than an essential form of xanthomatosis. As in hepatic xanthomatosis, the palms and soles are almost always involved in the process. *Xanthoma diabeticorum* is usually seen in patients who have a severe degree of diabetes which has been poorly controlled. The diagnosis of xanthoma diabeticorum is readily confirmed by the prompt involution of the cutaneous lesions that follows control of the diabetes by proper treatment.

Xanthoma disseminatum is a relatively rare condition. It differs strikingly from xanthoma tuberosum in that xanthomatous lesions occur on flexural surfaces rather than on extensor surfaces and predominate in the axillae (fig. 57b), groin and mucous membranes. There may be extensive involvement of the larynx and pharynx, necessitating tracheotomy. The blood cholesterol and total lipids are normal or even subnormal. Xanthelasma is also usually present. In addition, there may be a history of

diabetes insipidus and cases have been reported in association with Hand-Schuller-Christian disease with evidence of typical bony changes of that disease. Evidence of cardiovascular disease is lacking, although there may be hepatic involvement in the terminal phases. It must be kept in mind that in children there may be exceptions to the rule and, occasionally, a combination of tuberoso and disseminate forms of xanthoma appear in association with combinations of systemic involvement.

The *histopathologic changes* in the skin are similar in all the types of cutaneous xanthoma mentioned so far. These changes consist of deposition of lipids, especially cholesterol, in so-called foam or xanthoma cells (fig. 59). Touton giant cells predominate in lesions of xanthoma tuberosum and xanthoma disseminatum but are rarely found in lesions of xanthelasma. Cholesterol clefts and collections of cholesterol crystals may occur, especially in lesions of xanthoma tuberosum. So-called xanthic tumors of the tendon sheaths differ only in the predominance of fibrous tissue.

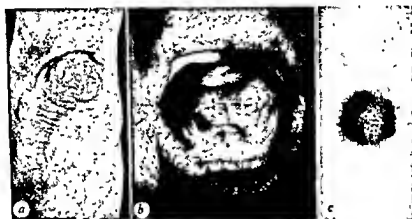


Fig. 60a.—Lipoid proteinosis. Lesions on elbow which lack a xanthomatous hue and resemble those of a plaque of localized neurodermatitis with lichenification. *b* Same case showing involvement of lips and sclerosis and binding down of the tongue. *c* Small plaque of necrobiosis lipoidica diabetorum from leg with yellowish center and reddish purple periphery.

There is a rare form of xanthoma known as *nevroxantho-endothelioma* occurring in infancy and consisting usually of a few xanthomatous papules or nodules which occur in a group but at times occur as multiple and extensive lesions. In this condition, there is no evidence of hyperlipemia or of systemic involvement and the lesions involute spontaneously in a few months, hence, this type of the disease is to be distinguished from juvenile xanthoma, which usually offers a serious prognosis. Nevroxantho-endothelioma can also be distinguished from juvenile xanthoma on the basis of histopathologic findings, as in nevroxantho-endothelioma there are endothelial giant cells as well as characteristic xanthoma or foam cells, including Touton giant cells.

An uncommon type of cutaneous xanthoma is known as *lipoid proteinosis*. The cutaneous lesions are seen on the elbows (fig. 60a) and knees in the form of lichenified papules and plaques resembling clinically localized neurodermatitis. The lesions do not have a yellowish or xanthomatous hue

and do not itch. The pharynx is often involved and there may be a sclerosing of the mucous membranes, pulling the tongue down (fig. 60b), both processes result in disturbance of speech and hoarseness. Diabetes has been reported in some cases and there is a definite tendency for the disease to be familial. There is no specific treatment. There seems to be a relative increase of the plasma phosphatides rather than of cholesterol; in this respect the disease resembles the Briger-Grutz syndrome but hyperlipemia is not present. The disease has the name "lipoid protomosis" because of diffuse extracellular deposits of lipids in the tissue without evidence of foam or xanthoma cells but with rather diffuse staining of the collagen fibers with the lipids. There is some question whether this condition should be included under true diseases of lipid metabolism or whether it simply represents a degenerative process.

This latter concept is probably true in *necrobiosis lipoidica diabetorum*, in which there are multiple yellow to red sclerotic plaques varying in size and occurring chiefly on the extremities (fig. 60c). There is associated diabetes in 90 per cent of the cases and 80 per cent of the lesions occur in women. Although the diabetes when present is usually of a severe grade, an occasional case is encountered in which there is no evidence of diabetes mellitus. The histopathologic picture of *necrobiosis lipoidica diabetorum* shows regions of pseudonecrosis of the connective tissue and regions of extracellular deposits of lipids. There is no response of the lesions to treatment.

There are several diseases of lipid metabolism of rare occurrence, of which *Niemann-Pick disease* is one. This usually occurs in infants but may occur at any age and is characterized by splenohepatomegaly. Although the skin has a distinctive yellowish hue, cutaneous xanthomas are seldom found. In this disease there is a disturbance of the phosphatide metabolism, especially of that of the diaminophosphatides (sphingomyelin). *Gaucher's disease*, which is equally rare, is characterized by enlargement of the spleen and liver, mothting and rarefaction, cortical thickening of the long bones, cuneiform thickening of the conjunctiva and a bronzing of the skin with or without scattered hemorrhages. Cutaneous xanthomas are not present. The disease is familial and the disorder has to do with disturbance of metabolism of kersin.

It has been customary in the past to group *Hand-Schüller-Christian disease* with systemic xanthomatosis and there still seems to be justification for this in that cases of *Hand-Schüller-Christian disease* and disseminate xanthomatosis have been reported occurring in the same individuals. Farber, Mallory and others, however, have called attention to the close relationship between *Letterer-Siwe disease*, *Hand-Schüller-Christian disease* and *eosinophilic granuloma of the bone* and they have noted that all types of transitions between these three conditions may occur. Furthermore, they believe that foam or xanthoma cells found in these conditions are a secondary degenerative phenomenon rather than a part of the essential pathologic process and that in the early phases of these diseases foam cells containing lipids are not demonstrable in tissue nor is there a hyperlipemia. Wallgren grouped *Letterer-Siwe disease* and *Hand-Schüller-Christian disease* under the term "*systemic reticulo-endothelial granuloma*" and this term might also include *eosinophilic granuloma of the skin and bones*.

The various forms of cutaneous xanthoma are readily diagnosed because of the distinctive yellowish to saffron-like color of the lesions. The distinction as to the type of xanthoma can be made on the basis of the distribution of the lesions and the concomitant blood lipid studies in addition to the evidence of systemic involvement. In *Letterer-Siwe disease*, petechial exanthems and purpuric lesions are frequently encountered. However, we have seen a mild form of this disease in a child in whom the cutaneous lesions clinically resembled those of disseminate xanthomatosis or disseminate ganglioneuroma but in whom the histologic changes in the skin and bone were those of eosinophilic granuloma. No foam or xanthoma cells were present and there was no hyperlipemia. The cutaneous lesions in *eosinophilic granuloma* of the skin have varied from superficial granulomatous lesions to lesions resembling *scrofuloderma* and bear no resemblance to xanthoma. The lesions in *urticaria pigmentosa* may present a yellowish hue but there is definite pruritus and urtication of the lesions can be produced. Cutaneous xanthomas are to be distinguished from multiple *cholesteatomas* and also from so-called *lipoid topi*, which resemble *gouty topi*. Distinction from so-called *yellowing dermatosis* (Weidman), including *senile elastosis* (fatty degeneration of elastic tissues), *pseudoxanthoma elasticum*, multiple *ganglioneuromas* of the skin and *Danlos' syndrome*, usually can be made by concomitant clinical and histologic findings. *Resorption xanthomas* represent fatty degenerative changes which are the sequelae of various granulomas or result from fatty degeneration in neoplasms. It is almost impossible to distinguish clinically and even at times histologically between fibrotic stages of solitary lesions of *xanthoma tuberosum* and the histiocytic phase of *nodular subepidermal fibrosis*. In the latter condition, however, there is not any increase of the plasma lipids. Most types of xanthoma may or may not be associated with *xanthochromia* and *carotinemia*.

Our knowledge of the etiology of diseases of lipid metabolism is dependent in part on our knowledge of the synthesis of the various lipids and much remains to be determined in this regard. The multiple concepts of the etiology of xanthoma have been discussed in papers by Thannhauser and Schmidt and by one of us (H.M.). Thannhauser and Magendantz spoke of a primary essential xanthomatosis which includes most types of cutaneous xanthoma, the *Hand-Schüller-Christian disease* group, *Gaucher's disease* and *Niemann-Pick disease*. They then recognized a secondary type of xanthoma due to *lipemia* in which the foam cells simply store excess of lipids as, for example, *xanthoma diabeticorum* and finally localized formation of xanthoma cells in true tumors. In the primary essential xanthomatosis, Thannhauser and Magendantz assumed that xanthomatous lesions, whether cutaneous or systemic, actually were responsible for increase of blood plasma lipids. It is difficult for us to conceive that a few cutaneous lesions in some cases of *xanthoma tuberosum* with hyperlipemia but without systemic manifestations can be responsible for the hyperlipemia. This would be equivalent to explaining an increase of the uric acid of the blood as the result of *gouty topi*. There are many other explanations of the cause of xanthoma and of hyperlipemia that have been offered in the past, none of which have been proved.

In regard to treatment and prognosis, the lesions of *xanthelasma* and

xanthoma tuberosum may involute partially or even completely after the ingestion of a diet low in fat and, more particularly, one free of animal fat. Reduction of the blood lipids in the liver occurs and it may, therefore, be anticipated that beneficial effects will follow a fat-free diet in regard to cardiovascular complications. Many other types of treatment have been advocated for xanthoma tuberosum but they have failed to prove their worth, except probably the use of small doses of thyroid in connection with a diet free of animal fat. Strangely enough, this diet proved of benefit in one case we had of xanthoma disseminatum in which the blood lipids were normal. The tumors may be surgically excised when they interfere with function. As mentioned previously, xanthoma diabeticorum responds promptly to administration of insulin and proper regulation of the associated diabetes. Roentgen therapy seems to be the treatment of choice in regard to the bone lesions in Hand-Schüller-Christian disease and related diseases. The prognosis in xanthomatosis is dependent on the type of involvement and the extent and severity of the systemic manifestations

TREATMENT OF SYPHILIS, WITH SPECIAL REFERENCE TO PENICILLIN*

PAUL A. O'LEARY

It is now known that the earlier treatment with penicillin is started in the course of the syphilis the better are the results. When treatment is begun during the seronegative chancre phase; that is, before the results of serologic tests have become positive, there is a likelihood of "cure" in 90 per cent of the cases. As the disease develops and when secondary lesions on the skin and mucous membranes are present the incidence of successful results decreases to about 70 per cent.

Therefore, effort should be made to start treatment as soon as the diagnosis can be made by darkfield examination of material from the chancre, and if the patient has passed through this phase of the disease, the serologic test of the blood and darkfield examination of material from the secondary lesions should be made before treatment is started. Even though a few days' delay in starting the treatment does slightly lessen the incidence of "cure," it is obligatory that the diagnosis be established by some definite means other than by the clinical impression before treatment is instituted.

Experience has shown that the best results follow use of a dose of approximately 3,500,000 units of penicillin, given intramuscularly at the rate of 50,000 units every three hours. This requires that the patient stay ten days in the hospital, which is at the present time the outstanding objection to this system of treatment. In addition, it has been found advisable to supplement the administration of penicillin with injections of mapharsen and bismuth, which may be given concurrently with the penicillin or before and

* Abstract of paper published in full in the *Journal-Lancet*, n.s. 68 96-99 (Mar.) 1948.

after it. At the present time at the Mayo Clinic we give an injection of mapharsen of 0.04 gm. on each of four successive days. On the fifth day administration of penicillin is started and when the afore-mentioned schedule is completed, an insoluble bismuth preparation is given at the rate of 1 c.c. every five days until twenty injections have been given.

The quantitative titer estimation adds materially in evaluating the result of treatment and is a satisfactory guide in determining the need for repeating the course of treatment described. The titer estimation of the blood reported in terms of units ranging from 3,600 to 0 gives a more graphic picture of the status of the infection than does a report of a strongly positive, positive or weakly positive result of a serologic blood test. In many cases of early syphilis the titer may be reported as 1,280, 640, 320 or 160 units and after treatment it may decrease gradually to 40, 20 or 10. A steady decrease of this type is a favorable indication and frequently by the sixth or eighth month after treatment the titer has been reduced to 0 and the results of serologic tests have become negative. In some cases the results of treatment are not so satisfactory in that the titer will be reduced to 10 or thereabouts, remain at that level for a few months and then begin to increase again up to 40, 80 or more. Such an increase is an unfavorable sign because experience shows that an increase in the titer strength usually precedes by several months a clinical relapse. Accordingly, titer estimations should be made at monthly intervals after treatment and when the titer remains stationary at 20 or 40 units for three months or when it shows an increase in strength, a second course of treatment identical to the first one should be given. The results indicate that by following such a procedure and not waiting until a relapse occurs, as indicated by recurrent lesions of the skin and mucous membrane, the effect of the second course of treatment is decidedly more favorable.

The regimentation of the treatment of early syphilis is not advisable. It is not expected that the condition in all cases will react similarly to the same amount of treatment, so that when evidence of failure is apparent or suggested, it is recommended that a second and, occasionally, a third course of treatment with penicillin, mapharsen and bismuth be given.

Mention has been made of the fact that hospitalization and a three hour intramuscular injection schedule are the drawbacks to penicillin therapy. In addition, complications such as urticaria, painful hips after injections and vesicular eruptions of hands and feet are annoying but not serious. The possibility of a Herxheimer reaction, the activation of a syphilitic lesion, should be borne in mind in cases of both early and late syphilis.

In an effort to simplify the procedure of treatment, Romansky and Rittman suggested the use of penicillin in beeswax and oil. Although this reduces the number of intramuscular injections to one a day for a period of ten to fourteen days, the results from this type of treatment are somewhat less satisfactory than those noted after the penicillin, mapharsen and bismuth system has been used. Investigations are under way to improve the results of use of the beeswax-oil combination and it may be that such an improvement will be described in the future, but until it is physicians must bear in mind that the better of the two methods is still the more inconvenient to both physician and patient.

The incidence of positive results of examination of the spinal fluid in

cases of early syphilis is lower after penicillin therapy than after any previously described treatment. This indicates that the incidence of clinical neurosyphilis may be reduced materially in a decade or two among patients who have received this type of treatment.

The results of the treatment of syphilis of the central nervous system have been less successful than the treatment of early syphilis. Favorable changes in the spinal fluid have been in my experience the most outstanding effect, while improvement in the clinical manifestations of *tabes dorsalis* and general paresis has been rather conspicuous by its absence. It has been necessary to use fever therapy in conjunction with penicillin for treatment of patients who had clinical signs of *tabes dorsalis* or general paresis and, contrary to the experience of others, I have not seen a remission develop in a case of general paresis after the use of penicillin alone.

Experience with penicillin therapy in cases of cardiovascular syphilis does not as yet warrant deductions. At least five years of treatment and observation of patients with aortic syphilis must elapse before it will be possible to estimate the results of penicillin therapy.

Probably the outstanding value of penicillin is in its ability to prevent the transmission of syphilis from the pregnant mother to the offspring. The reports have indicated that 95 per cent or more of the mothers who have syphilis and receive penicillin during their pregnancy have normal children. This also includes women who have recently-acquired syphilis. Three million units given during the last part of the first trimester is usually enough to prevent transmission of the disease to the child; however, if the mother's syphilis is acute, it is well to repeat a second course of penicillin at the beginning of the third trimester. It is somewhat paradoxical that, although the syphilis is not transmitted to the child, the mother is not always "cured." Also, it is recommended that women who have had syphilis for several years and are in the latent phase of the disease undergo a course of penicillin therapy during each pregnancy.

Unfortunately, the results from the treatment of the syphilitic newborn infant are not so satisfactory; likewise, the influence of penicillin on the retarded manifestations of congenital syphilis, such as interstitial keratitis, is not great enough to warrant its use. In such cases it is still advisable to use mapharsen and bismuth in conjunction with fever therapy. Fever may be induced with typhoid vaccine, malaria or the fever machine.

The treatment of latent syphilis with penicillin has been discouraging thus far. In cases in which the patient has had syphilis for ten or more years, results of examination of the spinal fluid are completely negative and no evidence of cardiovascular involvement can be recognized, the use of penicillin has been of slight benefit in reversing the positive results of serologic tests.

RECENT ADVANCES IN DERMATOLOGY AND SYPHILOLOGY*

LOUIS A. BRUNSTING

In recent years there have been many significant developments in the field of dermatology and syphilology, some of them of far-reaching importance in relation to systemic disease, others of direct value to the practicing physician in the management of the patient.

TOPICAL APPLICATIONS

In dermatologic treatment, topical applications such as ointments and lotions play a large role. Some of them are used for their own value as lubricants but more often they are used to convey medicaments to the diseased skin. The choice of vehicle is an important one, for in certain conditions a surface action is desired, in others, a penetrating effect. Many new types of creams and emulsions have been made possible by the utilization of such recent materials as synthetic resins and waxes, bentonite clay and the various wetting agents. Physicians now have available a wide range of emulsions, greases, greaseless bases, interface active agents to facilitate penetration, protective creams and efficient soap substitutes. The quaternary ammonium salts (phenimerol, zephiran) are useful detergents but their antiseptic action is neutralized by soaps.

ANTISEPTICS

Dermatologists have long objected to the use of cresol, mercurials and iodine as preoperative skin antiseptics because of their high sensitizing properties. A new bactericidal agent which will be of interest to surgeons has been incorporated in a soap (G-11 soap); in clinical trials it has proved to be nonirritating to the skin and to possess unique antiseptic properties.

SULFONAMIDES, PENICILLIN AND STREPTOMYCIN

The treatment of superficial pyogenic infections of the skin such as impetigo, ecthyma and folliculitis was thought to be solved with the introduction of the sulfonamides and, later, penicillin and streptomycin. However, subsequent experience has shown that the sensitizing capacity of these drugs is such that they are not fit for general use in such cases, at least not by topical application. Tyrothricin, on the other hand, is quite useful and is relatively nonirritating when used as a lotion or a moist compress.

Ten years of experience with the systemic administration of sulfonamides has shown that the usefulness of these agents in dermatologic conditions is somewhat restricted. Of course, they are still valuable in cases of severe streptococcal and staphylococcal infections in which penicillin is ineffective or because the patient is sensitive to it or the organisms are penicillin-fast. In chancreoid infection, sulfadiazine or sulfathiazole is the drug of choice. In the early stages of lymphogranuloma venereum, a long period of treatment with sulfadiazine is indicated. Sulfapyridine seems to have a specific

* From the Alberta Medical Bulletin 17: 20-25 (Oct.) 1947; Canadian Medical Association Journal 55: 153-157 (Feb.) 1949.

effect on the control of the symptoms of dermatitis herpetiformis but its prolonged use is not without hazard.

The systemic use of penicillin is indicated in erysipelas, erysipeloid, carbuncle, cellulitis, lymphangitis and other severe and deep seated streptococcic and staphylococcic infections of the skin such as hidradenitis suppurativa. Streptomycin has a limited application in dermatology; it is indicated in those pyogenic infections which are penicillin-fast; it is effective in early tularemia and perhaps in granuloma inguinale; it has proved promising in certain cases of ulcerating cutaneous tuberculosis. On the other hand, the systemic reactions attending the prolonged use of streptomycin in sizable doses, particularly the damaging effect to the vestibular apparatus and the eighth nerve, as well as the expense of administration, are serious drawbacks. The use of penicillin and streptomycin has proved disappointing in the treatment of pemphigus and disseminated lupus erythematosus.

SCABIES AND PEDICULOSIS

A few other items of interest in the treatment of dermatologic conditions may be mentioned briefly. The most effective agent for treatment of scabies and pediculosis is the formula of Eddy: benzyl benzoate 10.0, DDT (dichlorodiphenyltrichloroethane) 1.0, benzocaine (ethyl aminobenzoate) 2.0, tween 80 (Atlas Powder Co.) 2.0 and water in sufficient quantity to make 100.0 (all in terms of grams or cubic centimeters). This emulsion is rubbed liberally into the affected parts on two occasions, twelve hours apart.

CONDYLOMATA ACUMINATA

These moist warts respond to one or more applications of podophyllin powder used as a 25 per cent suspension in mineral oil. Some prefer a 20 per cent suspension of the powder in 95 per cent alcohol to limit better the caustic to the lesions themselves and to minimize the irritation of adjacent membranes. Ordinary warts and plantar warts are not affected by podophyllin. Sullivan and King have shown that podophyllin exerts a specific effect on cell structure similar to that produced by colchicine.

FUNGUS INFECTIONS

In dealing with fungous infections of the feet, it is well known that certain persons are particularly susceptible while others seem to be relatively immune. This difference is due in part to the fact that certain fatty acids in the sweat and other secretions of the skin are natural inhibitors of the growth of fungi. In accordance with this principle, preparations of undecylenic and propionic acids have been developed for therapeutic purposes and in extensive clinical trials in military and civilian practice they seem to have lived up to expectations. They are quite mild, even after protracted use. They are not cure-alls, however, and they will not replace conventional remedies during the acute stages of infection, nor will they eradicate obscure foci from the nails. Their chief virtue lies in the prevention of infection, and when applied conscientiously as powders to the feet they are a safe and efficient prophylactic.

Fungous infections of the scalp in school children are another matter, especially those due to *Microsporon audouinii*. Thousands of such cases

came to light in the metropolitan centers coincident with the shifting of large numbers of industrial workers during the war. The only efficient cure for ringworm of the scalp, except by the occurrence of puberty, is by roentgen epilation of the scalp. The use of topical fungicides is tedious and disappointing although promising results were reported with two such preparations, trimethyl cetyl ammonium pentaehlorophenate and salicylanilide. The reason why ringworm of the scalp is cured spontaneously at puberty is clarified by the work of Rothman, Smiljanic and Weitkamp, who demonstrated that certain fatty acids in the hair are fungistatic and that their inhibitory effect is five times more pronounced in adults than in children.

ANTIHISTAMINIC SUBSTANCES

Although the role of histamine in anaphylaxis and allergy is still controversial, by this time physicians are convinced of the value of antihistaminic drugs, such as benadryl and pyribenzamine in the symptomatic relief of urticaria, angioneurotic edema and certain other itching dermatoses. So far at the clinic we have observed no serious consequences from the use of either of these drugs, even with prolonged administration, although the common disagreeable side effects of drowsiness, dizziness and nausea may render certain persons intolerant to each of them. As a rule, drowsiness occurs more frequently with the administration of benadryl than with pyribenzamine, but this is not unwelcome in dealing with nervous patients or when the drug is given at bedtime. Pyribenzamine, on the other hand, is prone to cause excitement which interferes with sleep. We have observed a slight suppression of hematopoiesis in connection with its use. Pyribenzamine is somewhat effective as a local anesthetic when applied as a 2 per cent ointment in cases of localized pruritus about the anus or vulva.

No doubt, the present extensive program of research in this field will bring out other drugs more effective and less toxic than those now available. At the Mayo Clinic, my colleagues and I have had an opportunity recently to appraise such a new antihistaminic drug called "thenylene" (N-(alpha-pyridyl)-N-(alpha-thenyl)-N',N'-di-methylethylenediamine hydrochloride). Preliminary observations on seventy-eight patients with allergic dermatologic disorders who were given the drug by mouth in maximal dosage of 100 mg. four times a day indicate that it is safe and effective. In therapeutic efficiency it stands between benadryl and pyribenzamine but, with thenylene, unpleasant side effects were surprisingly few. The greatest benefit was in the relief of the symptoms of acute urticaria, but, as with the other drugs, the benefit to other itching conditions such as atopic dermatitis and contact dermatitis was disappointing. It is impractical to make a valid statistical summary of the effects of treatment on a subjective symptom such as pruritus. Some persons in this series expressed a preference for one or the other of the three drugs on the basis of apparent relief of symptoms and absence of side effects; this fact indicates that at present there is room for all three in clinical practice.

NITROGEN MUSTARD IN MYCOSIS FUNGOIDES

Preliminary observations indicate that nitrogen mustard is capable of bringing about improvement and temporary remissions in certain cases of mycosis fungoides as it does in other of the lymphoblastomas. The drug has

an extremely toxic effect on the hematopoietic system and in spite of certain dramatic responses in therapy it will probably find a limited application as an adjunct to roentgen rays. During the past year my colleagues and I have concluded, on the basis of our experience in treating nine patients who had mycosis fungoides with one or more courses of nitrogen mustard, that the drug is inferior to roentgen rays and is less safe, and that the chief indication for its use will be in those cases in which the disease is fulminating or in which a full quota of roentgen therapy has been applied or in which the disease appears to be refractory to such treatment.

VITAMIN D₂ (CALCIFEROL) IN LUPUS VULGARIS

Vitamin therapy in diseases of the skin, as in general medical conditions, has been much overdone. Aside from its use in such obvious deficiencies as pellagra, scurvy and perhaps in Darier's and Devergie's diseases, the indications for such treatment have been decidedly limited. During the war years, however, a remarkable advance in the treatment of lupus vulgaris by the prolonged administration of large doses of vitamin D₂ was brought forth independently by Fanielle in Belgium, Charpy in France and Dowling and Prosser Thomas in England. This treatment has been found effective within one to three months in a high percentage of cases of lupus vulgaris and in other forms of cutaneous tuberculosis as well, although, at the same time, the older procedures of local measures and systemic support have not been ignored. Vitamin D₂ (calciferol), with or without the addition of milk or calcium salts, is given by mouth according to various schedules for a long period of months; Hasebiek and Michelson recommended 1,000 to 2,000 units per kilogram of body weight per day. In dealing in such quantities, untoward effects and hypercalcemia may be expected in 25 to 35 per cent of such cases, but with proper selection of patients and careful supervision, serious complications seem to be surprisingly few. The mode of action of vitamin D₂ on cutaneous tuberculosis is not known, whether the effect is on the bacillus, the skin or the general system. Curtis and co-authors have applied the Charpy treatment in sarcoidosis with some encouragement; they postulate a possible influence on phospholipid metabolism.

PENICILLIN IN THE TREATMENT OF SYPHILIS

In this short discussion I can only summarize briefly the current status of penicillin in the treatment of syphilis for it will take another decade or two before valid conclusions can be drawn as to the over-all efficacy of schedules and combinations of drugs. Treatment around the clock may be replaced if penicillin in oil and beeswax proves effective. So far, as physicians we have made the strategic error of underestimating our opponent; we have given too little treatment; we have expected too much of the drug without respecting the resistance of the patient, as in the latent stages of the disease or under conditions of parenchymatous damage; finally, we have minimized the valuable auxiliary role of the arsphenamines, bisinuth and fever.

For detailed instruction in regard to technic of present schedules I can recommend to you the bulletin of the Veterans Administration on the management of syphilis.

In the treatment of early syphilis, penicillin is highly effective and the

shorter the duration of the disease the better the results. At present it is our opinion at the clinic that a combination of penicillin with oxophenarsine hydrochloride and a bismuth preparation given either before or after or concurrently offers the highest rate of success. Such patients should be followed regularly after treatment with clinical and serologic examinations in order to anticipate relapse. It is well to remember, too, that the small dose of penicillin needed to cure gonorrhea may serve to delay the signs of a concurrent syphilitic infection for several months.

Benign gummatous lesions of the skin and bones respond well to penicillin, likewise gummatous hepatitis and gastric syphilis respond.

Syphilis in pregnancy is an ideal condition for the use of penicillin and reports indicate that such treatment has seldom failed to prevent syphilis in the offspring. A course of penicillin may be used even late in pregnancy if the child is viable. Pregnant women with syphilis should receive at least 2.4 million units of penicillin, perhaps more, and at the clinic we prefer to give such a course in the first trimester and again at the seventh month.

Penicillin is more effective in congenital syphilis of infants and young children than in older children but the results are variable. A course of seven and a half days of treatment at three hour intervals is recommended, a total dose of 100,000 to 400,000 units per kilogram of body weight being utilized. Interstitial keratitis is refractory to penicillin.

In neurosyphilis there is an excellent response in cases of asymptomatic infection and syphilitic meningitis. In vascular neurosyphilis the response is equivocal but the treatment is relatively safe. In parenchymatous types of neurosyphilis, the longer the duration and the more the damage, the less the degree of clinical improvement. The most pronounced effect of penicillin in cases of neurosyphilis is on the cerebrospinal fluid; the effect is, first of all, on the pleocytosis and total protein, later, on the colloidal curve and the serologic reaction. Tabetics often gain weight and improve in other respects after a course of treatment with penicillin. Patients who have optic atrophy and general paresis need treatment with penicillin and malaria.

In cardiovascular syphilis penicillin should be used with caution. In late latent syphilis and in so-called Wassermann-fast cases there is no evidence that penicillin is of value.

BAL (BRITISH ANTI-LEWISITE)

This is a dithiol compound (2, 3-dimercaptopropanol) which was developed during the war in a search for antivesicants. BAL has strong affinity and binding power for heavy metals, particularly arsenic and mercury, and it has been applied effectively in the treatment of intoxications by these drugs. In the treatment of syphilis, BAL is a valuable prophylactic to be used at the first sign of intolerance to the arsphenamines. It has been shown to influence markedly the morbidity and mortality rates in arsenical exfoliative dermatitis and hemorrhagic encephalitis, providing the toxicity has not been established too long. BAL is given by intramuscular injection in dosage of 2.5 to 3.0 mg. per kilogram of body weight at four hour intervals the first forty-eight hours and in decreasing doses thereafter for the next ten days. Physicians who use arsenical drugs in the treatment of syphilis, and mercurials as diuretics should have access to a supply of BAL to be used at the earliest signs of untoward reaction.

THE TERMINATION OF THERAPEUTIC MALARIA WITH CHLOROQUINE*

ROBERT R. KIERLAND AND WILLIAM G. MCCREIGHT

Chloroquine is one of a series of preparations investigated in recent years for the treatment of malaria. The chemical formula is 7-chloro-4 (4-diethylamino-1-methylbutylamino) quinoline diphosphate.† The drug previously carried the experimental number SN 7618. Earlier investigative work by Most and his co-workers showed this drug to be of definite benefit in the treatment of acute relapsing attacks of malaria caused by the *Plasmodium vivax*. They were of the opinion that the interval between attacks of relapsing malaria is longer than when atabrine (quinacrine dihydrochloride) is used and that the drug is better tolerated than atabrine.

Most and his associates noted that in 20 per cent of cases pruritus developed sometime in the course of treatment while some type of erythema, urticaria or a mild papular eruption developed in 2.4 per cent. Mild and transient headaches, visual disturbances and gastro-intestinal symptoms also have been noted.

This report deals with the use of chloroquine in the termination of therapeutic malaria in twenty-five cases.

All of the patients in this group were inoculated with malaria for the treatment of syphilis of the central nervous system. The ages of the patients ranged from twenty-three to fifty-seven years. The strain of organisms has been in use for more than twenty years and is of the tertian type, *Plasmodium vivax*. The mode of inoculation was direct from patient to patient by the intravenous injection of 5 c.c. of whole blood. The blood was taken from a donor only after it had been demonstrated that *Plasmodium vivax* was present in the peripheral blood by examination of thick smears.

Neither the incubation period nor the number of paroxysms of malaria could be shown to have any effect on the results obtained with chloroquine. The incubation period of malaria varied from one to twelve days. Each patient had not less than seven nor more than ten paroxysms before termination was attempted.

Chloroquine was used as the only antimalarial drug in all twenty-five cases. The dosage and method of administration were as follows: 1 gm. followed in six hours by 0.5 gm., then 0.5 gm. again in twenty-four and forty-eight hours. The total dose in twenty-three cases was 2.5 gm. and in two cases, 3 gm. When the medication was given to the patient after his temperature had receded to 103° F. or lower the chance of vomiting was less. Furthermore, it was noted that there was less likelihood of an additional paroxysm when the drug was given during the fall of temperature. In twenty-one cases no febrile episodes occurred after administration of the drug was started, while in four an additional paroxysm occurred within twenty-four hours. In these four cases use of the drug had been started during a paroxysm while the temperature was ascending.

* From the American Journal of Syphilis, Gonorrhea and Venereal Diseases, 32: 57-58 (Jan.) 1918.

† Chloroquine used in this study was supplied by the Winthrop Chemical Company, New York City, New York.

Only one patient reported a side reaction. This was a mild gastrointestinal upset and was transient, lasting less than twenty-four hours. Pruritus, urticaria or evidence of dermatitis did not develop.

Blood smears were examined for plasmodia after administration of chloroquine in fourteen of the twenty-five cases. In two cases plasmodia had disappeared within twenty-four hours after the initial dose of the drug was given; in four, within forty-eight hours, and in seven within seventy-two hours. In one case plasmodia were found until the fifth day. In one case smears were made repeatedly but no plasmodia were found throughout a typical malarial course and the patient's temperature returned to normal promptly after the administration of chloroquine. To our knowledge relapse of therapeutic malaria has not occurred two to eight months after treatment with chloroquine.

AN EVALUATION OF THENYLENE HYDROCHLORIDE (N, N-DIMETHYL-N'-(ALPHA-PYRIDYL)-N'-(ALPHA-THENYL) ETHYLENEDIAMINE HYDROCHLORIDE)*

ROBERT R. KIERLAND AND ROBERT T. POTTER

A clinical evaluation of thenylene, a new drug with antihistaminic properties, shows it to be of definite value in treatment of certain dermatologic conditions. Its most marked effect was in treatment of dermatoses, such as urticaria and angioneurotic edema which are characterized by cutaneous edema. With few exceptions oral doses of from 50 to 100 mg. three or four times a day led to lessening or disappearance of such edema. No cumulative effect was noted and untoward reactions were minimal. A clinical comparison of the results of treatment with thenylene, benadryl and pyribenzamine revealed a high degree of similarity.

THE USE OF NITROGEN MUSTARD IN THE TREATMENT OF MYCOSIS FUNGOIDES†

ROBERT R. KIERLAND, CHARLES H. WATKINS AND C. C. SHULLENBERGER

The treatment of leukemia, Hodgkin's disease and lymphosarcoma has been advanced materially by the addition of the β -chloroethyl amines (the nitrogen mustards) to the other methods of therapy used in these conditions. To this group of diseases which have a common generic term of "lymphoblastoma" belongs the condition known as "mycosis fungoides." It is natural then that such a drug should be used in the treatment of mycosis fungoides and already preliminary reports are appearing concerning its value.

* Abstract of paper published in full in the *American Journal of the Medical Sciences* (In press.)

† From The Journal of Investigative Dermatology, 9:195-201 (Oct) 1947.

It has been suggested that the method of action of the nitrogen mustards is the inactivation of the essential cellular enzymes. On the basis of various studies, it has been shown that the phosphokinases are highly susceptible but that this sensitivity also is found in other types of enzymes. There is no definite correlation between susceptibility in enzyme systems, *in vivo* and *in vitro*. Inactivation of cellular enzymes by nitrogen mustard is probably not the primary process.

Many systemic effects can be produced in mammals by the administration of toxic amounts of the mustards, but small doses produce pathologic changes, chiefly in cells and tissues which are proliferating actively. As a result of the latter observation, it has been concluded that the mustards frequently exhibit a primary nucleotoxic action and that they act directly on the chromosomes without much influence on other cellular activities, to produce an inheritable chromosomal abnormality. This latter effect has not been demonstrated with any other group of chemical compounds. floentgen and ultraviolet rays are the only other known agents which will produce inheritable chromosomal abnormalities. Evidence also indicates that in certain tissues, a cytoplasmic change occurs, which results in necrosis of the cell. While toxic doses bring about widespread changes, minimally effective doses evoke pathologic changes only in cells and tissues normally exhibiting a high rate of growth and proliferation. The mitotic arrest seems confined to the resting stage of the mitotic cycle so that the total effect is to deplete the tissue of mitotic figures.

The marked effects of the β -chloroethyl amines on lymphoid tissue and the observations that hyperplastic tissues are susceptible to the cytotoxic action of these compounds suggested their therapeutic use.

The formed elements of the blood and the gastro-intestinal mucosa are the first to reflect the cytotoxic action of the nitrogen mustards. The action on the hematopoietic organs is reflected by lymphopenia, granulocytopenia, thrombocytopenia and anemia in the order named. The lymphopenia is usually apparent within twenty-four hours after the first injection and is progressive for six to eight days. The count of the lymphocytes usually returns to normal two to three weeks after the last dose. The total count of leukocytes declines progressively for two to three weeks after a course of treatment. This decrease is due to neutropenia in addition to the lymphopenia. Within three weeks after the maximal reduction, the neutrophil count is usually back to normal. Thrombocytopenia usually appears during the third week after treatment; the platelet count at that time ordinarily falls to between 60,000 and 100,000 per cubic millimeter of blood.

The effect on the gastro-intestinal system is usually apparent within four hours after an injection and is manifested by nausea and vomiting which is seldom prolonged. These manifestations are most noticeable after the first one or two injections and often do not appear after the later doses. Diarrhea occurs occasionally.

DOSAGE AND OBSERVATIONS IN SIX CASES

The form of nitrogen mustard used in this study was methyl-bis (β -chloroethyl) amine hydrochloride. The drug was administered intravenously; a single dose was 0.1 mg. per kilogram of body weight. A course of treatment consisted of four such doses given on successive days. The

decision to employ subsequent courses depended on the clinical response, the condition of the patient and the status of the hematopoietic system.



Fig. 61a.—Before treatment with nitrogen mustard. Note the delineated area across the lumbar region exhibiting the improvement (on the left) from roentgen therapy six weeks previously. No roentgen therapy was given to the sacral area and buttock. b. Two and a half months after treatment with nitrogen mustard. The resolution of the tumors of mycosis fungoides is evident. There had been a recurrence of lesions in other areas.

Additional courses were not given sooner than six weeks after the preceding course. The individual doses which our patients received varied from 4.5 to 8.5 mg.

To date we have treated six patients who had mycosis fungoides with nitrogen mustard. Three of the patients have had two courses of the drug.

One patient died of a febrile illness unexplained on necropsy two weeks after a course of treatment with nitrogen mustard was given. This patient had never received roentgen therapy. The infiltrated plaques of mycosis fungoides showed regression within one week after the completion of the course of treatment.

Another patient (fig. 61) because of pregnancy, received roentgen therapy to all the skin except that on the lower part of the back and abdomen. Benefit was noted in all irradiated regions. One month after roentgen therapy, a normal infant was delivered. Two weeks later a course of treatment with nitrogen mustard was given. Within two days after completion of this course of treatment, the pruritus improved and within a week there was regression in the size and degree of infiltration of the tumors in the regions which had not been treated with radiation. The patient returned two and a half months later for another examination. Although her condition was improved as compared with that on the original examination, there were new tumors and recurrence of nodules in some regions. She then was given a second course of nitrogen mustard.

Four of the patients in this group had received repeated courses of roentgen therapy over a period of one to six years. The plaques and tumors of mycosis fungoides had become resistant to radiation in these cases and for this reason nitrogen mustard was administered. The results of treatment in one case were striking. The patient rapidly gained in strength and weight, while the pain and pruritus almost completely disappeared. The infiltration and erythema of the skin rapidly subsided so that she was able to return home after continuous hospitalization for ten months. She returned for a second course of nitrogen mustard six weeks later. At this time her general condition was still improving but the paroxysmal pruritus had recurred. The general condition and cutaneous lesions of the three other patients improved after treatment with nitrogen mustard. One patient who had two courses of treatment reported increased pruritus following the second course after having had relief of pruritus after the first course. However, the lesions of mycosis fungoides were disappearing and there were no new lesions two months after the second course. Relief of pruritus was great in the other two cases one to two and a half months after treatment. They did not have any new lesions and improvement in the original lesions continued (fig. 62). As this paper was being finished, two patients returned two and seven weeks, respectively, after the original follow-up. Both have had mild recurrences of infiltrated plaques and moderate pruritus.

Four of our six patients had universal exfoliative erythroderma in addition to the other evidences of mycosis fungoides. Following treatment with nitrogen mustard the exfoliative dermatitis improved rapidly in two cases and slowly in two. Improvement in the generalized eruption did not begin as soon as, or progress as rapidly as, the improvement in the infiltrated plaques and tumors, although relief of pruritus was the first beneficial effect noted by most patients.

Reactions to nitrogen mustard in our cases were essentially of the gastrointestinal type. All patients had nausea after the first injection and four had vomiting within three hours after the first injection. As the injections were continued daily, the nausea and vomiting tended to become less severe; however, it was necessary to discontinue the daily injections in two cases

because of the severity of the reaction. Diarrhea occurred in one patient. Pyridoxine administered intravenously seemed of some value in decreasing the severity of nausea and vomiting.

Disturbances of the formed elements of the blood are seen frequently in patients treated with nitrogen mustard. In our patients leukopenia, granulocytopenia and thrombocytopenia occurred. However, in no instance did the count of the leukocytes drop to less than 2,500 per cubic millimeter of blood. In one case the platelet count fell to 48,000 per cubic millimeter but



Fig. 62a.—Before treatment with nitrogen mustard. *b*. Two and a half months after treatment with nitrogen mustard. Note the almost complete disappearance of the infiltrated plaques. Excoriations are less.

rose promptly. No patient required treatment because of the temporary suppression of the function of the hematopoietic system. In those patients whom we were able to follow closely for some time, the factors of the blood became normal three to four weeks after treatment. In no patient was it necessary to discontinue therapy for more than two days because of any untoward reaction.

In these four cases in which specimens for biopsy were taken before treatment was instituted, histopathologic changes were typical for mycosis fungoides in either the infiltrated or tumor stage. There was no histologic

evidence of lymphosarcoma or Hodgkin's disease. Biopsy of specimens taken at varying intervals after treatment with nitrogen mustard revealed relatively little change in the *histologic picture on comparison with the picture before treatment*. No correlation could be made between the histologic picture and the degree of clinical improvement.

In one case there was some decrease of the infiltrate with some increase of pyknosis and karyorrhexis of the cells two weeks after treatment. In two other cases, specimens for biopsy, taken late after treatment (seven weeks and two and a half months), still showed clear-cut evidence of mycosis fungoides and little change was noted in the character of the infiltrate. In one case a *third biopsy one day after a second course of treatment disclosed no appreciable change in the degree of infiltrate or in the character of the individual cells as compared to observations made at the first biopsy and at one made two and a half months after the first course of treatment*.

It is obvious that an adequate histologic study of the therapeutic influence of nitrogen mustard on the lesions of mycosis fungoides must entail more biopsies of specimens from the same lesion and similar lesions at more frequent intervals in order to determine the period of maximal therapeutic response and the average duration of remissions.

COMMENT

Treatment of mycosis fungoides by means of methyl-bis (β -chloroethyl) amine hydrochloride appears to produce the same effect and to bring about the same clinical result as does roentgen therapy. Goodman and his associates have suggested that responsiveness to therapy by radiation occasionally may be restored after a course of treatment with nitrogen mustard. We have not been able to demonstrate this because of the limited period of observation in our cases. Yet there is no doubt that nitrogen mustard is an adjunct to therapy when the lesions of mycosis fungoides have become resistant to roentgen therapy.

No patient was treated with both nitrogen mustard and roentgen rays at the same time; in one case nitrogen mustard was given six weeks after an intensive course of irradiation without any more untoward reaction than one would expect from the drug alone.

The gastro-intestinal reactions from nitrogen mustard are more acute and at times more severe than is seen with roentgen therapy; yet the patients recover more rapidly from their reactions. It seems too, that the recovery of the hematopoietic system is more rapid after treatment with *nitrogen mustard than after radiation*.

It is impossible from this study to determine the duration of remissions produced by treatment with nitrogen mustard. In two of our patients they have lasted slightly more than two months and in one more than four months. However, two of these three patients had two courses of treatment. It is probable that longer remissions will be seen as the period of observation lengthens. Whether or not remissions from the use of nitrogen mustard will be as lasting as those produced by radiation is a question that cannot be answered by the material available at present.

The first evidence of benefit noted by the patient was a diminishing of the pruritus followed shortly by an increase of the sense of well-being. Usually within a week after the last injection the tumors and nodules be-

came softer, as did the infiltrated plaques. The erythroderma became less vividly colored and assumed a dull hue.

SUMMARY AND CONCLUSIONS

Methyl-bis (β -chloroethyl) amine hydrochloride (nitrogen mustard) has been used for the treatment of mycosis fungoides in six patients. In four of these patients the condition had become resistant to roentgen therapy.

One patient died of apparently unrelated causes shortly after a course of nitrogen mustard was given. The general condition and the cutaneous lesions of the other five patients improved significantly after treatment. Three patients have had two courses of the drug.

The duration of remissions obtained with this therapy are impossible to predict but in one patient a remission of more than four months' duration has been obtained.

Reactions are frequent, acute and occasionally severe, but in all cases it was possible to complete a course of therapy without serious ill-effects.

The limited histopathologic findings indicate to us that the response of the individual lesions in the same individual and of lesions of different individuals to therapy with nitrogen mustard will vary greatly.

Nitrogen mustard in the treatment of mycosis fungoides is an adjunct to previously recognized therapeutic measures and is of particular value when roentgen therapy is no longer of benefit.

THE ARTERIOLES OF THE SKIN IN ESSENTIAL HYPERTENSION*

EUGENE M. FARBER, EDGAR A. HINES, JR., HAMILTON MONTGOMERY AND WINCHELL McK. CRAIG

It is generally accepted that a diffuse disturbance of the arterial side of the vascular system exists in hypertension. Curiously enough, the cutaneous arteriolar beds in people with essential hypertension have not been studied adequately. For this reason, we felt that a controlled study of the arteriolar bed of the skin in a group of persons who had essential hypertension might be of value.

METHOD

In order to determine the degree of thickening of the arteriolar walls and the alteration in the diameter of the lumens, measurements were made according to the method followed by Kernohan, Anderson and Keith in their study of the arterioles of the pectoral muscle. A Bausch and Lomb micrometer eyepiece was used over a high-power objective, which produced a magnification of 430 times (43×10). With this instrument the average diameter of the wall of the vessel and of the lumen was measured. We studied every slide from left to right, and made measurements of the first four arterioles we saw in each slide.

* Abridgment of paper published in full in *The Journal of Investigative Dermatology*, 9:285-298 (Dec.) 1947.

In the material obtained for biopsy from people who had normal blood pressure, fewer arterioles were apparent than in the material secured from members of the hypertensive group. It is conceivable that hypertensive arterioles of the skin are so tortuous that the same vessel may be sectioned several times in one preparation.

MATERIAL

Material for this study was obtained from the upper arm, lumbar region and the calf of fifty-two persons who had normal blood pressure and from seventy persons who had moderate to severe essential hypertension. The skin was obtained by means of excision and punch. All the material in the hypertensive group was secured from living people. The youngest hypertensive person was twenty-nine years old; the oldest person was eighty years old; the mean age was forty-four years. Of the fifty-two specimens of skin removed from persons who had normal blood pressure, forty were taken from living people and twelve were obtained at necropsy.

The Section on Pathologic Anatomy sent us specimens of skin from the upper arm (at the junction with the shoulder girdle), and from the leg, obtained from the twelve persons with normal blood pressure who came to necropsy. The relative wall-to-lumen ratio of vessels in the skin obtained from postmortem material was essentially the same as the wall-to-lumen ratio of vessels in skin secured from living patients with normal blood pressure.

All tissue was fixed in formaldehyde U. S. P. (1:10), blocked in paraffin and stained. Four stains were used: hematoxylin and eosin stain, elastin-H stain, van Gieson stain and the elastin-van Gieson stain.

It is well known that a chronic inflammatory reaction may produce thickening of the arteriolar wall. Hence, only normal-appearing skin was studied.

The adventitia was not included in determination of the outer diameter of the arteriole. In this study, the outermost cells of the media were used to define the external diameter.

There is no widely accepted definition of an arteriole. Maximow and Bloom referred to arterioles as "the smallest arteries, i.e. 300 microns or smaller." Evans defined an arteriole as an artery with a media of two to three muscle cells in thickness. Kernohan and associates used the measurements of 25 to 100 microns to delimit the arterioles in their study. We have employed their criteria, and have measured vessels with diameters in this range. Most of the arterioles were located in the deeper portion of the cutis. Not infrequently, arterioles varying from 25 to 40 microns were found adjacent to dermal appendages.

QUALITATIVE CHANGES OF ARTERIOLES AMONG HYPERTENSIVE PERSONS

Although thickening is characteristic of the hypertensive arteriole, it was not present in nine of our seventy patients who had essential hypertension. This observation parallels the findings of Moritz and Oldt, who also observed normal arterioles in some persons who had long-standing elevation of the blood pressure. It was apparent that the arterioles of hypertensive patients have thicker walls than are those of nonhypertensive

patients. Careful study of each arteriole revealed structural changes similar to those found in the arterioles in other organs of persons with hypertension. Endothelial hyperplasia, proliferation and thickening of the inner elastic lamina were frequently present. Hyperplasia of nuclear elements in the media also was present. A reduction in the size of the lumen, periarteriolar fibrosis and occasional thrombotic occlusion likewise were observed.

We did not make a statistical analysis of the qualitative changes in the arterioles. In this study it was apparent that not all arterioles were equally affected; nonetheless, a large percentage showed some change from the so-called normal arteriole. In our series there was no appreciable difference in a comparison of the wall-to-lumen ratio of the arterioles of the group in the third to fourth decade and the group in the sixth to seventh decade of life. This also is in conformity with results of most of the investigations of arterioles in other organs in the hypertensive group.

RATIO OF WALL TO LUMEN OF THE NORMAL ARTERIOLE

Cutaneous arterioles from the arm, leg and back of fifty-two persons who had normal blood pressure were measured. The mean age of these patients was forty-four years; sixteen were women, thirty-six were men.

TABLE 1

MEAN RATIO OF WALL OF ARTERIOLES TO LUMEN, DIFFERENT REGIONS OF THE BODY, AS REPORTED IN VARIOUS STUDIES

Authors	Region	Ratio				
		Normal persons	Persons with hypertension of group			
			I	II	III	IV
Kernohan, Anderson, Keith	Pectoral muscle	1:2.00				1:1.1
Morlock	Pancreas	1:2.45				1:1.21
	Liver	1:2.51				1:1.13
	Gastro-intestinal tract	1:2.13				1:1.14
	Spleen	1:1.32				1:1.01
Wick	Myocardium	1:2.00				1:1.88
Rosenberg	Brain	1:3.50				1:1.70
Kyser	Thyroid	1:1.68	1:1.64	1:1.59	1:1.57	1:1.30
Cain	Kidney	1:1.82				1:0.70
Present authors	Skin	1:2.14	1:1.54	1:1.08	1:1.54	1:1.38

Skin from the Arm.—The lowest wall-to-lumen ratio was 1:1.39; the highest ratio was 1:3.00; the average was 1:2.13.

Skin from the Leg.—The lowest wall-to-lumen ratio was 1:1.43; the highest was 1:2.03; the average was 1:2.10.

Skin from the Lumbar Region.—The lowest wall-to-lumen ratio was 1:1.28; the highest was 1:2.66; the average was 1:2.20.

Mean.—The mean for the control group was 1:2.14 (table 1). These results are practically identical with the normal values other workers have found. Kernohan, Anderson and Keith considered the ratio 1:2.00 to be normal for arterioles in all tissues (table 1).

RATIO OF WALL TO LUMEN AMONG HYPERTENSIVE PERSONS

Cutaneous arterioles from the arm, leg and back of seventy patients who had essential hypertension were measured. The average age of these patients was forty-four years; thirty-five were women and thirty-five were men.

Skin from the Arm.—The lowest wall-to-lumen ratio was 1:0.82; the highest was 1:1.99; the average was 1:1.53.

Skin from the Leg.—The lowest wall-to-lumen ratio was 1:0.87; the highest was 1:1.69; the average was 1:1.29.

TABLE 2

MEAN RATIO OF THE THICKNESS OF THE WALL TO THE DIAMETER OF THE LUMEN OF THE ARTERIOLES OF NORMAL AND HYPERTENSIVE PERSONS

Biopsy, site	Normal persons		Hypertensive persons	
	Number	Mean wall-to-lumen ratio	Number	Mean wall to-lumen ratio
Arm	25	1:2.13	15	1:1.33
Leg	14	1:2.10	21	1:1.29
Back	15	1:2.20	34	1:1.76
All sites	52	1:2.11	70	1:1.57

Skin from the Lumbar Area.—The lowest wall-to-lumen ratio was 1:1.12; the highest was 1:2.78; the average was 1:1.76 (table 2).

Mean.—The mean for seventy cases was 1:1.57. The arterioles of the patients who had group IV hypertension were more profoundly altered than were those of patients who had hypertension of other groups. Thirteen patients had hypertension of group I, thirty-one had hypertension of group II, sixteen had hypertension of group III, ten had hypertension of group IV.

COMMENT

Although the arterioles in the skin of persons who had inalignant hypertension were more profoundly altered than were those of persons who had other types of hypertension, equally severe qualitative changes were present in the arterioles of a number of persons who had the other types of hyper-

tension. The duration and severity of the hypertension, as well as the fact that only one small portion of skin is under study, are variables which may influence the degree of arteriolar change.

Arterioles of the hypertensive patients and of those in the control series did not show any measurable difference in the wall-to-lumen ratio from youth to old age (table 3).

TABLE 3

AGE OF NORMAL AND HYPERTENSIVE PATIENTS AND MEAN RATIO OF THICKNESS OF WALL TO DIAMETER OF LUMEN OF ARTERIOLES

Age, years	Normal persons		Hypertensive patients	
	Number	Mean wall-to-lumen ratio	Number	Mean wall-to-lumen ratio
10-19	1	1:2.27	9	
20-29	7	1:2.17	5	1:2.41
30-39	9	1:2.09	17	1:1.68
40-49	13	1:2.14	32	1:1.59
50-59	14	1:2.22	11	1:1.41
60-69	5	1:1.87	5	1:1.09
70-79	2	1:1.95	1	1:1.21
80-89	1	1:2.01	1	1:1.70

In our group of normal controls there were four cases in which the wall-to-lumen ratio was decreased and medial hypertrophy was present. This suggests that arteriosclerosis was present in approximately 5 per cent of members of the control group in this study.

Nine of the hypertensive patients did not have arteriosclerosis, nor was there any decrease in the wall-to-lumen ratio of their arterioles.

CONCLUSIONS

A measureable thickening of the arteriolar wall and a decrease in the wall-to-lumen ratio as compared to normal were found in vessels of the skin of hypertensive patients. The average of the wall-to-lumen ratio of the arterioles of fifty-two persons with normal blood pressure was 1:2.14; among seventy persons who had essential hypertension it was 1:1.57. All arterioles were not equally affected in the same case.

Qualitative changes also were present. Hyperplasia of the nuclear elements of the media and thickening of the inner elastic lamina appeared to be the most common changes. Occasionally, complete occlusion of the lumen occurred. Four patients with normal blood pressure had medial hypertrophy of the arteriolar wall.

PORPHYRIA WITH CUTANEOUS MANIFESTATIONS*

LOUIS A. BRUNSTING AND HAROLD L. MASON

The changes that occur in the skin in chronic porphyria are these: melanosis, hypertrichosis, milia and a chemical and physical alteration of the connective tissue which renders the surface layers susceptible to trauma and gives rise to a blistering reaction to light. Only the exposed skin is so affected, presumably through the toxic influence of cumulative doses of light, although the blisters cannot well be reproduced by artificial means and cannot be reproduced at all on the skin that has been protected from light. These changes occur also in epidermolysis bullosa which is likewise an inherited abnormality of the skin, but the two conditions are entirely distinct. In epidermolysis bullosa, trauma alone is the precipitating agent and the pressure surfaces such as the palms and soles are primarily involved. It would be better to describe the cutaneous manifestations of porphyria as "bullosis actinica et mechanica."

In porphyria, even on the light-exposed surfaces, blistering is a late manifestation and the Nikolsky phenomenon can be elicited irregularly if at all. To some extent, the degree of cutaneous reaction in porphyria may be proportional to the concentration of porphyrins in the tissues and to the kind of porphyrin that is concerned, as well as to the nature and concentration of the light source and the effect of its cumulative action. Photosensitivity is prominent in those cases in which porphyrins are injected experimentally into the skin and in cases of congenital porphyria, but it is rarely a feature of cases of so-called acute porphyria.

One may speculate as to the role of the liver in the pathologic physiology of the skin in porphyria. The liver frequently is involved in acute porphyria. The changes in the skin in chronic porphyria may be influenced by the abnormal porphyrins which are produced when the liver is damaged by such a toxin as alcohol, for example; on the other hand, such a damaged liver may also serve to inhibit or destroy certain protective enzymes which are essential in the skin for the prevention of reactions of photosensitivity.

The chief protection of the skin against light is probably the keratin layer but the value of pigment cannot be dismissed summarily. The de-colored skin in vitiligo, for instance, is particularly susceptible to light and in congenital porphyria in cattle it is the white skin that manifests the photosensitive reaction. The production of pigment in the human skin, in cases of chronic porphyria, is probably a late effect and represents an effort to protect the underlying tissues from penetrating radiation.

Milia occur in the areas of skin that have been affected by light in chronic porphyria. They represent invaginated sebaceous accretions which may occur in normal skin about the eyelids and the genitalia or they may occur in the scarred skin in diseases such as pemphigus or epidermolysis bullosa or in old burns.

In recent years, physicians have become increasingly aware of the importance of the subject of porphyria. If careful search were made of mem-

* Abstract of paper read at the meeting of the American Dermatological Association, Murray Bay, Quebec, Canada, June 2 to 6, 1947.

bers of families in which isolated cases of manifest porphyria occur, it is reasonable to suppose that a reservoir of cases of latent porphyria would be uncovered.

ULCERS OF THE LEG IN MEDITERRANEAN DISEASE*

J. EARLE ESTES, EUGENE M. FARBER AND J. M. STICKNEY

Mediterranean disease, better known as Cooley's anemia, has been recognized as a distinct clinical entity for only a little more than two decades. In spite of this fact, an extensive literature on this comparatively rare disease has been developed and has recently been reviewed by Wolman and Dickstein. It was not recognized until recent years that Mediterranean disease occurred in adult persons as well as in children. What was formerly considered to be a severe, invariably fatal disease of childhood has been found to be a disease which has a great variation in severity. It may be so mild as to give rise to no clinical symptoms. A carrier state has been thought to exist so that although a person does not have symptoms of Mediterranean disease, he may pass on to his progeny a genetic trait which ultimately may result in a clinically recognizable form of the illness. Thus, Mediterranean disease can exist in a patient of any age, and it may be severe, mild or clinically detectable only by a thorough study of the blood.

Three adult patients who had Mediterranean disease of varying severity were studied at the Mayo Clinic in October of 1946. They were sisters of Italian descent; all three at one time or another had had ulcerations of the skin of the legs. A study of the literature on Mediterranean disease has failed to disclose mention of ulcers of the leg occurring in this type of anemia. It is the purpose of this paper to report ulceration of the skin of the legs as a manifestation of Mediterranean disease. Each of these patients stated that she had been anemic many years, and that a diagnosis of Cooley's anemia had been made many times.

The first patient was a thirty year old Italian woman who complained of soreness in the right upper abdominal quadrant. She had been informed by her local physician that she had gallstones. When she had been fourteen years old, ulceration of the skin over the medial aspect of the left ankle had developed. This had lasted about a year and had healed slowly, leaving a scar. During the general physical examination moderate pallor of the oral mucous membrane was seen. There was tenderness to deep palpation in the right subcostal region, and the tip of the spleen could be felt 4 cm. below the left costal margin. A small pigmented scar was seen over the medial aspect of the left ankle. There were no other significant physical observations. Except for the ulcers on the leg, this patient had not been incapacitated by her disease.

The second patient was twenty-three years old. She came to the clinic because of an ulcer of the skin on her right leg. When she had been twelve years of age, two ulcers over the midportion of the right leg had developed. These had lasted for two years and finally had healed, leaving scars. At

* From Blood 3,302-306 (Mar) 1949.

fifteen years of age an ulcer above the right lateral malleolus had appeared and had lasted for two years before it healed. At twenty years an ulcer had developed above the left lateral malleolus. This had been treated with balsam of Peru, but at the time of the examination it had not healed. In spite of long-existing anemia, in which the patient said the value for hemoglobin had averaged 8 gm. per 100 c.c. of blood for many years, she had not been incapacitated except by the ulcers of the leg. During the general physical examination a yellow pallor of the skin was noted. A systolic murmur was heard over the entire precordium. The spleen was palpable

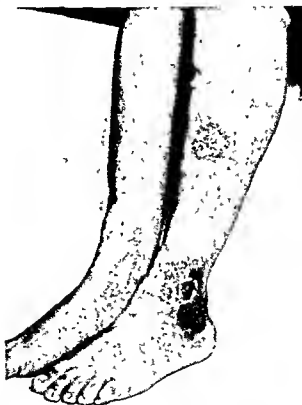


Fig. 63.—Indolent ulcer on the left leg of a female patient twenty-three years old who had Mediterranean anemia. Note the atrophic scars at the sites of old healed ulcers.

7 cm. below the left costal margin, and the liver was enlarged to a point 3 cm. below the right costal margin. An ischemic-appearing indolent ulcer 4 cm. in diameter was present on the lateral surface of the left leg above the external malleolus (fig. 63). The border of this ulcer was irregular, but was not undermined. There was considerable hyperpigmentation at the periphery of the ulcer, but in this zone there was only minimal cutaneous sclerosis. The base of the ulcer was clean. Three scars, the site of previous ulceration, were noted (1) on the right leg, (2) on the anterior surface of the left leg, in its upper third part and (3) on the lateral surface of the left

leg. These scars had a hyperpigmented periphery and a glossy, atrophic center. There were no other significant physical observations.

The third patient was nineteen years old. She came to the clinic because she had an ulcer on her right ankle which had remained unhealed for a year. When she had been seventeen years old an ulcer on the left ankle had developed which had been treated with penicillin without apparent effect. This ulcer had healed slowly over a period of eighteen months. A year later an ulcer on the right ankle had appeared and had been treated with halsam of Peru, but it had not healed.

During the general physical examination pallor of the mucous membranes and yellow pallor of the skin were noted. The heart was enlarged and the apical impulse could be palpated at the anterior axillary line. A loud blow-

TABULATION

RESULTS OF LABORATORY STUDIES: THREE PATIENTS WITH MEDITERRANEAN DISEASE

Test	Patient		
	1	2	3
Hemoglobin, grams per 100 c.c.	10.0	8.1	6.3
Erythrocytes, per cubic millimeter	4,240,000	4,140,000	2,870,000
Leukocytes, per cubic millimeter	10,900	11,500	6,300
Erythrocyte fragility in sodium chloride solution, per cent	.42 to .28 (Incomplete)	.46 to .28 (Incomplete)	.41 to .28 (Incomplete)
Beck and Hertz	No sickling	No sickling	No sickling
Serum bilirubin, milligrams per 100 c.c.			
Direct	0	0	0
Indirect	1.5	1.3	1.7
Fecal urobilinogen, milligrams (24 hour excretion)	109 169	183 269	223 244

ing systolic murmur was heard over the entire precordium, and it was maximal at the cardiac apex. Dyspnea was evident when the patient was at rest, and was pronounced after any exertion. The spleen extended to the umbilicus, and the liver was palpable 7 cm. below the right costal margin. A triangular ulceration of the skin 1.5 cm. in diameter was noted just distal to the right external malleolus. This ulcer was similar to the one described in the second patient. The present patient was suffering from a severe form of Mediterranean disease, and was greatly handicapped.

In none of these patients was there evidence of arterial or venous insufficiency in the extremities. Local treatment for the ulcers and the administration of iron, liver extract and whole blood had not brought about any improvement in the ulcers or the general health of the patients. In roentgenograms of the skull, only those of the third patient demonstrated

changes of significance. General osteoporosis, with thinning of both the inner and outer tables of the skull, was noted.

In smears of specimens of blood from all three patients similar changes characteristic of Mediterranean disease were seen. The changes were of a severity in proportion to the extent of the anemia. These changes consisted of a great variation in the size and shape of erythrocytes, with many microcytes but no spherocytes. Hypochromasia and polychromatophilia were marked, and normoblasts were present. Target cells were seen in all smears, but they were not conspicuous. Myeloid immaturity was not noted.

Studies of sternal bone marrow were made in each case. In all three there was hyperplastic erythropoiesis of the normoblastic type. Megaloblasts were not seen. It may be of some significance that the mature erythrocytes in the marrow smears were of more uniform size and shape than



Fig. 61.—Specimen taken for biopsy from the margin of an ulcer on the leg of a patient with Mediterranean anemia, showing dense deposits of iron in the midportion and lower portion of the cutis (hematoxylin and eosin $\times 25$).

were those seen in specimens of peripheral blood. Pertinent laboratory data are summarized in the tabulation.

The diagnosis of Mediterranean disease was made in these three cases on the basis of familial anemia, increased resistance of the erythrocytes to hemolysis in hypotonic solution of sodium chloride, very active normoblastic erythropoiesis, and the failure of the anemia to respond to any therapy. No other cause for the anemia could be found. Sick-cell anemia was eliminated by the absence of sickling, and congenital hemolytic icterus, had it been present, should have produced spherocytosis and increased fragility of the erythrocytes.

A piece of skin was removed for biopsy from the margin of the ulcer on the leg of the twenty-three year old patient. Epidermal changes consisted of minimal hyperkeratosis and irregular acanthosis. In the upper half of the cutis the capillaries and arterioles were increased in size and number,

and there was moderate infiltration of lymphocytes, connective-tissue cells, chromatophores and polymorphonuclear leukocytes. In the midportion of the cutis there were several areas of beginning necrosis with disintegration of cells, so that recognition of cell types in these areas was not possible. Elastic tissue was absent throughout the upper portion of the cutis, and very little elastic tissue was present in the vessels. Degenerative changes, homogenization of collagen and moderate edema were seen in the arteriolar walls. In occasional vessels there was proliferative intimal thickening, although in most of the vessels there was no significant alteration of wall-to-lumen ratio. Dense deposits of iron (fig. 64) were seen in the midportions and lower portions of the cutis stained with ferric thiocyanide.

The dense deposits of iron in these sections are of great interest. Whipple and Bradford have studied the deposition of iron-containing pigment in the organs of patients who died of Mediterranean disease. They considered this pigment to be as characteristic of the disease as is any other finding. It resembles that seen in hemochromatosis in adult persons and is seen in most of the organs of the body. Whipple and Bradford made no mention of such deposits in the skin. Mills has reported results of a postmortem study of the skin of a child who died of Mediterranean disease. He considered the pigment he found to be melanin, and not hemosiderin.

When the differential diagnosis of ulcers on the legs of these patients was considered, it was apparent that the lesions were not secondary to occlusive arterial diseases such as thrombo-angitis or arteriosclerosis obliterans. The absence of hypertension excluded the possibility of the ischemic type of ulceration occasionally associated with hypertension. Venous stasis could not have caused the ulcers because there were no varicose veins and chronic venous insufficiency was not present. Trophic disturbances such as might be caused by syringomyelia, tumor of the spinal cord or tabes dorsalis were excluded. Chronic granuloma as seen in syphilis, tuberculosis, sarcoidosis or dermatomycosis would have produced different histopathologic changes.

The ulceration of the skin of the legs which occurs in sickle-cell anemia and congenital hemolytic icterus do not have a distinctive gross appearance which could be used to distinguish them from each other or from those in the patients we are discussing. It seems to us that the chronic ulcer on the leg of an anemic patient is not pathognomonic of a specific type of anemia. The exact character of the anemia must be determined by appropriate clinical and hematologic study.

SUMMARY

Ulceration of the skin of the legs may occur in Mediterranean disease. Such ulceration cannot be distinguished grossly from that occurring in sickle-cell anemia and congenital hemolytic icterus. The outstanding histologic feature (noted at biopsy of one of these ulcers) is the prominent deposition of iron in the cutis.

THE MANAGEMENT OF ACUTE DERMATITIS*

HELEN JANE HARE

The management of acute dermatitis occasionally confronts almost every physician. By the term "acute dermatitis" is meant an acute, edematous, erythematous, vesiculopapular, weeping, crusting eruption which may occur from either internal or external causes.

The simplest reaction of the skin is that to a primary irritant. A primary irritant may be defined as a substance which will produce an inflammatory reaction on almost any skin. Poison ivy is a well-known primary irritant. A sensitizer, on the other hand, may be defined as a substance which is harmless to most persons but which will cause a cutaneous reaction in a few hypersusceptible persons. Nail polish may be cited as an example of a sensitizer.

Treatment of acute dermatitis is essentially the same, regardless of the causative agent. If the cause can be determined, this should be removed before treatment is instituted. The patient is usually acutely uncomfortable and, above all, desires relief from the pain and severe pruritus. Therapeutic measures should be as mild as possible. Wet dressings of a weak astringent or a mild antiseptic solution will usually offer the patient the greatest relief. A few of the mild wet dressings which are well tolerated are the following: 0.5 per cent solution of aluminum subacetate; half saturated solution of boric acid; 1:2,000 solution of silver nitrate; and physiologic salt solution. When secondary infection is present, 1:15,000 or weaker solution of potassium permanganate may be used. In cases in which vesiculation is marked, a hand or foot bath may be used in place of the dressings.

A wet dressing to be effective must keep the skin wet. This is accomplished by using a large amount of gauze held on by a bandage which is not too tightly applied and which is not covered by an impervious dressing. The upper and lower ends of the gauze should be loose enough so that the solution can be poured on at the open ends of the dressing every half hour or oftener. Removing the dressing every three to four hours and saturating it from a basin of the solution is advisable. If, when the bandage is removed, the gauze is stuck to the skin, it is obvious that the purpose of the wet dressing has failed and that no good has been accomplished. A complete change of the dressing should be made several times each twenty-four hours if inspection of the gauze reveals much purulent discharge.

The chief objections to wet dressings are the waterlogging of the skin and the danger, especially in the case of elderly patients, of catching cold. These objections can usually be overcome by removing the dressing for half an hour every six hours and allowing the skin to dry out.

The failure of wet dressings to produce relief when properly applied may be due to one of the following factors: the solution may be too strong, its pH may be too low or too high, or the dermatitis may still be in the process of spreading. When these situations arise, the type of application may be changed or weaker dilutions may be used and mild sedation given. Acetylsalicylic acid by mouth, grains 5 (0.3 gm.), four times daily will serve to

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relieve the intense pruritus. Sedatives of the barbiturate type should be avoided because of their tendency to produce cutaneous eruptions. The use of the new antihistamine preparations, such as benadryl and pyribenzamine hydrochloride, has been found helpful. The side effects of benadryl should be pointed out to the patient and he should be warned against driving a car while under the influence of the drug.

In treating a patient who has dermatitis which involves most of the body, the pruritus is often best relieved by having the patient immerse once or twice a day in a bath of cornstarch and soda or in a bath containing boiled oatmeal-soda gruel in a bag.*

As the vesiculation and edema subside and the process becomes less acute, use of the wet dressings may be discontinued and a mild ointment applied. Some of the preparations which might be used are 3 per cent ichthyol in either zinc oxide or aquaphor, equal parts of aquaphor and lime water or calamine lotion, followed, when it has dried, by boric acid ointment. Should the ointment cause any discomfort, it is usually advisable to return to the use of the wet dressings for two or three periods of several hours each.

Caution is necessary in the use of keratolytic agents. Their use is indicated only when the lesion of the skin is chronically thickened, dry and lichenified, and not when it is moist from vesiculation. Even when such agents as salicylic or benzoic acid are indicated, it is advisable to use them in weak concentrations. Either 1 per cent of *pix liquida* or 1 per cent of liquor carbonis detergens may be incorporated in a suitable base during this phase of the disease. Local applications containing mercurial salts, sulfur, resorcinol and local anesthetics, such as ethyl aminobenzoate, should be avoided due to their sensitizing properties.

Sulfathiazole and sulfadiazine by either topical or internal use for a time proved to be two of the most effective remedies available for the treatment of superficial pyogenic infections of the skin. Gradually, however, it was realized that these drugs were potent sensitizers without and within. In view of this discovery, their use has become limited to but a few dermatologic conditions in which they are highly specific. Penicillin, likewise was found to be highly effective locally, either in the form of wet dressings or when incorporated into an ointment. Further observations have revealed that it, too, contains highly sensitizing properties. Hence, its use has become restricted to the more serious systemic disorders.

It is not advisable to give injections of foreign proteins, such as vaccine, antigens and serums, to patients who have acute vesicular dermatitis. Such agents will be tolerated in some instances but more often severe accentuation or even complete generalization of the dermatitis may follow their administration. The use of poison-ivy antigen has been recommended by some physicians as a therapeutic agent but its use on occasion has been followed by a rapid spreading of the eruption to involve the whole body.

* *Cornstarch and soda bath.*—Make a cold water paste of 1 cup of cornstarch and $\frac{1}{2}$ cup of baking soda. Put this paste into about $\frac{1}{2}$ tub of warm water.

Collod bath.—Boil 2 cups of bulk oatmeal in 1 quart of water for thirty to forty-five minutes in a double boiler. Allow to cool for fifteen minutes, then add $\frac{1}{2}$ cup baking soda. Pour the entire mixture into a gauze bag and tie shut. Place in $\frac{1}{2}$ to $\frac{3}{4}$ tub of water at about 90° to 96° F. Patient may stay in the tub one half to two hours expressing the oatmeal mash through the gauze and applying it over the body.

It should be emphasized that the skin of a patient who has acute dermatitis is hyperreactive or hypersensitive and a number of medicaments which, under normal conditions, are well tolerated, will produce in an abnormal skin a severe aggravation of the dermatitis. This may occur not only in the involved parts but may be noted also on almost any part of the patient's skin. Although the mechanism of hypersensitivity is not too well understood, it might be well to comment on the part it plays in the result of local measures used in the treatment of acute dermatitis. Such a reaction is frequently noted when a patient consults a physician shortly after the onset of the dermatitis and the wet dressings applied give no comfort. Applications of wet dressings of several types for two to three days likewise fail to relieve the pruritus and all the while the dermatitis is spreading. This failure to respond to treatment is frequently the result of the increasing hypersensitivity and it is during this period particularly that the local use of strong applications will aggravate the condition. Four or five days or longer may be required for the dermatitis to reach its peak. During this time wet dressings of weak solutions of various types may be used. When relief finally is obtained, the last application employed is usually given the credit for controlling the dermatitis. In reality the improvement occurs because the process of hypersensitization has reached its peak and most of the types of local application which previously failed will now help the patient. The appreciation of this phenomenon is of utmost importance in the care of the patient who has acute dermatitis.

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HEAD, TRUNK AND EXTREMITIES

CAUSES AND TREATMENT OF EXOPHTHALMOS*

WILLIAM L. BENEDICT

Exophthalmos is only a sign of disease; it is never meaningless nor insignificant. It is an early sign in the course of so many local and systemic diseases that a classification of them into categories is required for a clear conception of that part of the syndrome attributable to exophthalmos.

EXOPHTHALMOS CAUSED BY CERTAIN TYPES OF EXTRA-ORBITAL LESIONS

Extra-orbital tumors and cysts which invade the orbit by direct extension produce exophthalmos as the first clinical sign of their development. From the bony walls of the paranasal sinuses, benign tumors called "osteomas" may extend into the orbit. They are usually rounded masses of cancellous bone with hard smooth shells; they consist of masses of mucus-filled cells and bony granules divided by thin septa. The tumors are pedunculated and covered by mucous membrane continuous with the lining of the sinus from which they spring. As they expand they cause erosion of the bones of the orbit and the adjacent sinus walls. The tumors covered with mucous membrane are in a potentially infected field continuous with the sinuses and are walled off from the brain and orbital tissues by an inadequate protective barrier.

Exostoses arise from the bones of the cranial vault. Those which arise from the inner surface of the frontal bone extend into the brain as pointed darts and set up local points of inflammation and thickening of the meninges but seldom penetrate the orbital roof.

Another type of bony tumor, hyperostosis, is the result of invasion of bone by a soft-tissue tumor, such as meningioma. A rare form of primary bone disease that involves all the bones of the head is leontiasis ossea. In acromegaly also the involvement of bones of the face is widespread and exophthalmos is not produced.

Congenital atresia of the connections of the sinuses with the nares or their closure in early life because of trauma or inflammation results in the formation of mucocoeles that alter the walls of the orbit and thereby produce exophthalmos and usually lateral displacement of the eyeball. Mucocoeles develop slowly in young persons and displace normal bony walls of the face and head, resulting in displacement of the eyeball and some exophthalmos with little or no visual disturbance. During the development of mucocoeles some walls are merely thinned by erosion so that the structural changes found on exploration are not evident on roentgenologic or rhinoscopic examination.

* Abridgment of paper published in full in the *Mississippi Doctor*, 25:59-64 (July) 1947. Also in the *Chicago Medical Society Bulletin*, 49:41-45 (July 19) 1947.

EXOPHTHALMOS CAUSED BY INTRA-ORBITAL LESIONS

• Closely resembling the changes in the orbit caused by mucocoeles are those caused by venous aneurysms and expansive lesions of the blood vascular system, such as hemangiomas and varices with arterial communications. Congenital varices or aneurysms are not common but congenital anomalous vessels are often noted from which aneurysms develop later in life.

Pulsating exophthalmos is due only to the flow of arterial blood into venous spaces. The most common cause of pulsating exophthalmos is fracture of the base of the skull and rupture of the cavernous sinus. A severe blow on the temple which luxates the petrous tip of the temporal bone is the most frequently recorded trauma. Evidence of occurrence of pulsating aneurysm may not appear for some days or weeks after the injury; this delay is a matter of medicolegal importance.

Vascular tumors of the orbit are related to aneurysms only in respect to the cavernous spaces found in certain types of angiomas which increase resistance to blood flow. Only a few of the large and most cavernous types of hemangiomas are found to be pulsatile; they differ from the common pulsating aneurysm in that the force of the pulsation is not accentuated by lowering the head.

Hemangioma is the most common primary tumor of the orbit and varies in size and density. Some are encapsulated and firm, with relatively scanty blood supply. They are known as "fibrohemangiomas" or "hemangio-fibromas," according to whether the fibrous mass or the blood spaces are dominant in the structure. Vascular tumors of any type within the orbit, whether primary or not, may cause exophthalmos. As such tumors expand, the exophthalmos usually progresses in proportion to the rate of growth of the lesion. However, congenital aneurysms are known to remain stationary for years.

Within the orbit may be found any type of tumor that can reach it by direct extension or by metastasis. Consequently, in any case of exophthalmos a thorough search for an extra-orbital tumor is required. Presence of a tumor within the orbit cannot always be excluded from the diagnosis, even though the evidence may be rather clear that the exophthalmos is explainable on other grounds; it should be remembered that intra-orbital tumors or cysts may be accompanied by signs of systemic disease.

EXOPHTHALMOS OF HYPERTHYROIDISM

It is estimated that exophthalmos occurs in about one of four persons who have hyperthyroidism. The degree of exophthalmos is somewhat indicative of the severity of the disease, although exophthalmos may be severe in quiescent cases of goiter and absent in severe cases. Ocular signs of goiter are usually bilateral and so, are quickly recognized. Unilateral occurrence of exophthalmos is often attributed mistakenly to orbital tumors. The time of appearance of exophthalmos in the course of the disease also is variable. In many cases in young persons, exophthalmos is the first and most prominent sign of the disease, while in older persons it may come on as a late sign, even after the usual systemic signs of goiter have subsided or disappeared.

A history of a transient episode of hyperthyroidism with complete recovery from systemic signs and symptoms can frequently be elicited by

Careful questioning in cases of exophthalmos that seem to have no other explanation.

TREATMENT

Treatment of exophthalmos may be considered under three headings: medical, radiation and surgical.

Medical.—Treatment of exophthalmos without resorting to surgery is applicable where the cause of the exophthalmos cannot definitely be determined, in cases of orbital cellulitis, and in systemic diseases in which inflammatory exophthalmos occurs as a complication. Proptosis with disturbance of motility and varying degrees of inflammation within the orbit is found in many cases of tularemia. Inasmuch as the diagnosis cannot be made from the ocular findings alone, every person exhibiting exophthalmos with a low-grade inflammation of the orbit should be given tests for tularemia. Streptomycin is most effective in the treatment of tularemia and causes the exophthalmos to recede within a few days. In the absence of positive tests for systemic disease such as tularemia, administration of antibiotic agents has not yielded good results. Only in cases of cellulitis of bacterial origin is exophthalmos relieved by the use of sulfonamides alone or sulfonamides combined with antibiotic substances.

Radiation.—Employment of radiation has a dual purpose. Exophthalmos may be caused to disappear by two or three treatments with roentgen rays. The diseases of the orbit which most commonly respond are Mikulicz's lymphosarcoma, chronic inflammation and the exophthalmos associated with goiter. If the exophthalmos is not altered by roentgen therapy, one may assume that the cause of the exophthalmos is other than one of the known conditions which usually respond. The delay incident to a trial of roentgen treatment is counterbalanced by the influence on the tissues exerted by the roentgen rays, so that in cases of inflammation or neoplasms in which the lesions are not susceptible to roentgen treatment the tissues may be sufficiently altered to retard further development of the disease. If satisfactory results are not obtained, roentgen treatments should not be long continued in cases of progressive exophthalmos unless surgical intervention is, for some reason, contraindicated. Roentgen therapy may be given to the orbit with little risk of causing blindness to occur as a result of cataract. Treatment may be given at intervals of several weeks if precautions are taken to protect the eyeball. In exophthalmos of hyperthyroidism, roentgen therapy has been found to be effective only in the malignant type of exophthalmos and then only in the early stages of the exophthalmos before permanent tissue changes have brought about so much fibrosis that full recession of the eyeball can hardly be expected.

Surgical.—The method to be used in the surgical treatment of exophthalmos is determined by the situation of the lesion and its character. Neoplasms of the orbit that lie in the anterior half may be reached by frontal approach through the orbital outlet. Of the many methods of orbitotomy that have been employed, only two are in common use.

An approach to the orbit through the palpebral fissure requires a wide external canthotomy. After retracting the upper lid the upper cul-de-sac is divided and the approach made through the orbital tissues in the superior temporal quadrant. The cornea is exposed during this operation and the eyeball is subject to permanent damage from trauma.

The frontal approach is made through a brow incision that divides the periosteum 5 mm. above the superior orbital rim. The periosteum is then carefully separated around the orbital margin where it is more firmly attached and where it meets the periorbital. Once the periosteum is separated at the orbital rim, the entire periorbital of the superior wall and most of the lateral and nasal walls can easily be separated by a nasal septum elevator. The periorbital can then be pulled forward and downward, permitting digital exploration of the contents of the orbit before the periorbital is opened. An incision through the periorbital can be made and oftentimes a tumor removed without cumbersome manipulation of extruded orbital fat. By this method 90 per cent of the tumors that lie in the anterior half of the orbit can be removed. This approach is followed by the least deformity and disfigurement from contracting scars.

The method described by Krönlein consists of a lateral orbital decompression which provides access to the posterior part of the orbit. For removal of tumors situated in the posterior half of the orbit, such as tumors of the optic nerve, the Krönlein method offers, in some cases, advantages not obtained by any other method.

Within the past few years, transcranial approach to the orbit has become the method of choice for aneurysms, certain types of orbital neoplasms, most neoplasms situated in the posterior part of the orbit and for orbital decompression for malignant exophthalmos. The transcranial approach has the advantage of providing visual exposure of the contents of the posterior half of the orbit and the optic canal. Meningiomas of the orbit should be removed only by the transcranial route because of the involvement of the orbital walls and extension into the cranial cavity. Arteriovenous aneurysms, pulsating angiomas and cavernous angiomas should be operated on only by the transcranial route. In cavernous angiomas the vessel walls are so thin that uncontrollable hemorrhage is likely to occur unless a surgeon has access to the full length of the orbital vessels. Ligation of the common carotid and its branches in the neck may not be sufficient to control an orbital hemorrhage in pulsating exophthalmos, and in nearly all such cases operation should be performed only by transcranial approach.

Orbital decompression for relief of exophthalmos in hyperthyroidism may be accomplished by removal of the roof of the orbit, exposing the dura, or by removal of the lateral bony wall so that the contents are supported by the temporal muscle. Both methods are effective in suitable cases. Malignant exophthalmos with edema of the lids and chemosis may be steadily progressive even after decompression. In such cases this operation is not suitable. The transfrontal exploration of the orbit carries sufficient hazard to contraindicate its use in cases of exophthalmos of unknown cause unless the exophthalmos is advanced to a dangerous degree or is producing definite visual deterioration.

One should bear in mind that exophthalmos is sometimes present in malignant hypertension and in chronic, low-grade inflammatory disease of the orbit with negative systemic findings. Exploration of the orbit in such cases is futile. The use of exploratory instruments, such as the trocar, in exophthalmos is never helpful and in many cases causes definite harm or complications that later become troublesome. Surgical exploration of the orbit should be undertaken only for the complete eradication of the cause

and not for the purpose of obtaining specimens for biopsy. The exercise of restrained judgment in the selection of the type of treatment to be employed in cases of exophthalmos of undetermined origin will prevent many costly mistakes.

TREATMENT OF RETROBULBAR NEURITIS BY OPERATION ON THE HYPOPHYSIS*

WILLIAM L. BENEDICT

Scotomata in the field of vision caused by lesions of the optic nerve indicate by their size and position the portion of the nerve involved, and to some extent the nature of the lesion can be presumed by variations in the intensity of the scotomata and the change in their form and size as the lesion progresses or regresses.

Whether the initial lesion in the optic nerve is due to inflammation or to pressure without inflammation, the phenomenon of visual loss as indicated by scotomata in the visual field properly may be considered as a sign of retrobulbar neuritis. Under the term "retrobulbar neuritis" are included a number of pathologic conditions due to various causes, some of which are remedied by medicinal means while others require surgical intervention. The latter will be considered in this paper. In order to clarify the distinction, a few comments on retrobulbar neuritis in general are appropriate.

DIAGNOSIS

The diagnosis of retrobulbar neuritis is made in the presence of indications of recent pathologic processes of the optic nerves which have interfered with or obstructed the transmission of visual impulses so as to cause blindness of all or a part of one or both eyes.

By means of a history or by records of previous examination, a loss of vision must be established consistent with our knowledge of the processes of inflammation and degeneration of nerve fibers due to pressure and other causes of atrophy. Optic neuritis as distinguished from optic atrophy is an active progressive change in viable nerve fibers as opposed to the unchanging static condition of fibers whose function can never be restored. It may be assumed that retrobulbar neuritis always precedes optic atrophy, whether due to inflammation, toxic poisoning or pressure. The loss of vision in an eye with a normal fundus justifies the diagnosis in the early stages of the visual loss regardless of the cause.

Optic neuritis subsides in any event. There is either recovery of function or atrophy of the affected nerve fibers with total permanent loss of function. Just how much damage can be imposed on the nerve and for how long and still be followed by recovery is the important factor in any case, and the wide differences are the characteristic of the etiologic factors. In the clinical examination of a patient with retrobulbar neuritis, the time when

* Abridgment of paper read at the meeting of the Third Pan-American Congress of Ophthalmology, Havana, Cuba, January 4 to 10, 1915.

function is irrevocably lost and atrophy sets in cannot definitely be determined by tests of visual function or by ophthalmoscopic inspection of the nerve head, although it is only by such measures that optic atrophy can eventually be determined. There is a marked difference in the probability of recovery of vision in cases of toxic poisoning due to lead, tobacco, methyl alcohol, quinine, neocarsphenamine, thallium, the bacterial toxins that result in localized inflammatory processes, the demyelinating diseases and pressure blocks that may result in necrosis.

The preliminary considerations of history of loss of vision and tests of residual function must lead to a conclusion of vitality of the nerve fibers as against atrophy before one can justify the diagnosis of retrobulbar neuritis. It is assumed that once resumption of vital function by the nerve fibers is lost the diagnosis of retrobulbar neuritis is no longer tenable and treatment is no longer indicated.

It is because of the difficulty in determining just when all hope for recovery is to be abandoned that the time for ceasing treatment must be determined on the basis of clinical experience. Clinical experience has shown the high rate of rapid and complete blindness in some of the forms of toxic poisoning, such as those due to quinine and methyl alcohol, and the slow recovery of vision in cases of amblyopia caused by alcohol or tobacco. So also, there is now available, through a series of closely studied and reported cases of partial blindness, some clues which one may follow in the proposed surgical exploration of the hypophysis with confident expectation of restoration of visual function, although vision may have been severely impaired for a considerable time.

Loss of central vision is an early sign of retrobulbar neuritis. It occurs as the initial symptom in 15 per cent of the cases of multiple sclerosis. When it is seen for the first time late in the course of disease, the diagnosis must rest largely on the history of the development of the scotoma. If central vision is lost within three or four days after the onset and the scotoma is large and central, the cause is most likely multiple sclerosis, assumed merely on the basis of probability, as multiple sclerosis is the most common cause in the recorded cases of retrobulbar neuritis. Next in order come toxic neuritis, tumors and hemorrhage. Acute optic neuritis most frequently occurs among young adults, owing to the high incidence of multiple sclerosis in this age group. Recovery of vision within two weeks is the rule.

The distinction between toxic and nontoxic types of retrobulbar neuritis is not always easy. The most common cause, multiple sclerosis, produces no other signs in 15 per cent of primary attacks. Multiple sclerosis was found in 45 per cent of a series of more than 500 cases of retrobulbar neuritis in which the patients were observed at the Mayo Clinic. The diagnosis was presumptive in a large number but in no case of retrobulbar neuritis presumed to be due to multiple sclerosis but not supported by other signs at the time was the cause ultimately found to be anything else.

The course of an episode of retrobulbar neuritis due to multiple sclerosis is short, two to six weeks. Recovery is not materially hastened by treatment but often is made more complete. In practically all cases of toxic neuritis also the disease is acute in onset and within a few days or weeks leads to permanent blindness or subsides with recovery of more or less vision.

In cases in which the neuritis is due to multiple sclerosis and in those in which it is due to acute toxemia, the clinical course is similar; however, it is quite different from the course in cases in which the disease is due to pressure about the hypophysis. The distinction is made largely by the history of the onset of blindness and the shifting pattern of the visual field as the scotomata enlarge and coalesce. In cases in which the neuritis is due to pressure about the hypophysis, the disease is characterized by signs of slowly progressive loss of function, a depression of visual acuity, relative scotomata, and quantitative changes in the field of vision, which in the beginning indicate suppression of function rather than blocking. Quantitative perimetry is of most value in cases in which retrobulbar neuritis is due to pressure on the optic nerves.

In most cases of retrobulbar neuritis the optic papilla is white after recovery. The degree of pallor of the disk is, however, no indication of the extent of recovery of vision. The appearance of the disk may be that of atrophy of the optic nerve except for the thickness of the nerve, that is, the "loss of substance" that characterizes atrophy. A pale nerve head that shows no nerve substance indicates atrophy of the optic nerve but, if nerve substance can be seen, atrophy has not yet made restoration of vision impossible. Even though vision is very poor or nil, the ophthalmoscopic appearance of the fullness of the disk rather than the color is the most important factor that prompts surgical intervention.

CHIASMAL LESIONS

In any case of retrobulbar neuritis the site of the lesion along the visual pathway is important. If the findings indicate that a lesion is situated about the region of the hypophysis, its cause and nature may be inferred by certain peculiar functional findings together with roentgenograms of the region.

When the vision of only one eye is involved in retrobulbar neuritis and that of the other eye is normal, it is evident that the affection is localized along the optic nerve of the affected eye, anterior to the chiasm. The cause and the nature of the lesion still must be determined. An episode of retrobulbar neuritis in a person who has previously had only one seeing eye is a tragedy from the standpoint of localization of the lesion and seriousness of the situation for the patient. It often occurs, however, in cases of chiasmal lesions. It is even possible for complete atrophy of one optic nerve to be followed by retrobulbar neuritis of the other nerve after some months or years, owing to the same cause, such as a pituitary tumor. The possibilities run the gamut of congenital anomalies, slowly progressive expanding growths, recurrent vascular accidents, remote results of trauma, repeated episodes of systemic infection and complicated situations in which a number of such causes may be involved simultaneously. Decisions in such cases must be influenced by circumstances. Treatment may be empirical, and radical procedures probably can be justified. The recognized and accepted syndrome of chiasmal lesions need not be reviewed at this time, but certain important findings that are lost sight of in routine clinical practice may properly be brought to mind as early diagnosis depends on recognition of early localizing signs. Subjective sensations of visual disturbances, such as evanescent episodes of visual impairment, transient scotomata, varying

in extent and severity, may occur for some time before perimetric studies are made. In such a case, the progress of the visual disturbance, once it is charted, can be followed by delineation of the scotomata, by periodic variations in visual acuity and by other findings relative to the disorder. In most cases, the disease follows a characteristic pattern which points to both the nature and the situation of the lesion when the patients are observed long enough. The danger of permanent damage to the optic nerves by prolonged subjection to a necrotizing lesion prompts early interference; therefore it may be necessary or prudent to perform surgical exploration in some cases, even though the diagnosis is only presumptive.

In the region of the hypophysis there are three conditions which may block the function of the optic nerves in such a way as to produce signs of retrobulbar neuritis of a slowly progressive type. The first and most common is a tumor of the pituitary body, the so-called pituitary adenoma; the second is a *vascular anomaly of the circle of Willis, such as an aneurysm or hemorrhage*, and the third is a tumor of the meninges, brain, and sphenoid sinus or ethmoid sinus.

The ocular symptoms and signs produced by pituitary tumors were summarized by W. I. Lillie as follows: (1) lowered central visual acuity; (2) pallor of the optic disk or simple optic atrophy; (3) bitemporal hemianopsia for various colors or for all colors; (4) bitemporal hemianopsia for form and colors; (5) bitemporal scotomatous hemianopsia for colors or form, or for both; (6) temporal hemianopsia with amaurosis of the opposite eye; (7) temporal hemianopsia with successive changes that lead to amaurosis, such as central scotoma, cecentral scotoma, enlargement of the scotoma, with islets of vision and amaurosis; (8) homonymous hemianopsia scotoma for colors or form, or for both; (9) homonymous hemianopsia for colors, and (10) homonymous hemianopsia for form and colors. In contrast to the symmetry of defects of the visual fields produced by lesions of the optic tracts or the optic radiations, visual defects produced by pituitary tumors, whether bitemporal or homonymous in type, are asymmetrical. It is generally believed that bitemporal hemianopsia of form and color is the typical visual defect in cases of pituitary tumor; however, the early changes in the visual fields which take place during the development of bitemporal hemianopsia are not individual types but constitute stages of an advancing process due to *changing pressure foci during the growth of the pituitary body*. While lateral hemianopsia is not rare in cases in which neoplasms have their origin in the hypophysis or in cases of pituitary disorders, too often the absence of bitemporal hemianopsia defers the localization of the lesion. This homonymous defect of the visual field occurred in only 6 to 7 per cent of each of several series of cases reported in the literature.

The region of the hypophysis is clearly outlined in roentgenograms which are of great help in diagnosis when bony changes are portrayed. The characteristic flattening of the sella turcica and the erosion of the clinoid processes are found in most cases in which the tumor has been present for a long time. They are regarded as indicating a benign type of tumor. Since erosion of bone takes place slowly when due to pressure alone, rapidly growing tumors may not be visualized roentgenologically. In cases of rapidly growing tumors of the pituitary body, the defects of the visual

fields progress rapidly. In the presence of a rapidly progressing defect of the visual fields, one would suspect that the patient had a malignant tumor.

The relation of the optic chiasm to the circle of Willis makes it susceptible to injury by pressure of the communicating artery where it crosses the optic tract midway and below, as was pointed out by de Schweinitz and verified by Lillie. Lillie reported four cases in which the arteries of the anterior portion of the circle of Willis produced a definite groove in the optic chiasm and caused changes in the visual fields. The loss of vision which resulted from optic atrophy due to pressure by the vessels in Lillie's cases leads one to take a more pessimistic attitude toward cases of this kind even though the tumor is completely removed and the chiasm is relieved of all previous pressure and distortion.

In cases in which visual disturbances have suggested the presence of a lesion situated in the region of the optic chiasm, an exploratory operation has disclosed an unsuspected tumor of the meninges in this region. Indirectly, pressure from a tumor of the meninges may push the chiasm against the vessels of the circle of Willis. In one case, exploration along the sphenoidal ridge revealed a large meningioma which arose from the tuberculum sellae turcicae and compressed the left optic nerve well laterally and the right optic nerve toward the base. The right ophthalmic artery had been grooved into the right optic nerve by the tumor which, as it grew, compressed the chiasm and right optic nerve against the ophthalmic artery and caused almost complete separation of the nerve.

RETINOPATHY OF MULTIPLE SCLEROSIS*

C. WILBUR RUCKER

A distinctive sheathing of the veins in the retina of some patients afflicted with multiple sclerosis was described by the author in 1944 and 1945. As far as he knows, this is the first time that this change had been ascribed to multiple sclerosis. Previously, it seems to have been regarded as a congenital anomaly. The time seems opportune to evaluate this condition in the light of its appearance in patients examined since the early reports, and to determine the diagnostic reliability of a possible retinopathy of multiple sclerosis.

Such a retinopathy would include pallor of the optic disks, since retrobulbar neuritis occurs commonly in multiple sclerosis and optic neuritis occurs occasionally, but since pallor can occur in so many other diseases it must remain incidental, and not a vital part of the retinopathy. The question arises as to whether venous sheathing alone can be accepted as indicative of a retinopathy of multiple sclerosis.

DESCRIPTION OF THE RETINAL VENOUS SHEATHING

It must be emphasized that we are not dealing herein with cuffing of the retinal veins, for which there is an obvious cause in the retina, such as

* From the Transactions of the American Ophthalmological Society 45:564-570, 1947.

occurs in hypertensive or diabetic retinopathy, uveitis and phlebitis, or vascular cuffing which forms near a patch of healed choroiditis or near the optic disk after papillitis.

The sheathing of concern herein appears around veins some distance away from the optic disk, and for no obvious reason. It never involves the retinal

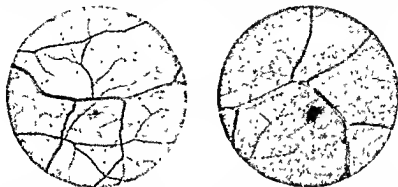


Fig. 65a and b—Two views of the superior temporal vein of the left eye, showing moderately thick sheathing visible as a white line on either side of the column of blood. The proximal and peripheral limits of the sheathing are evident. (The dark spot below the center of each picture is an artefact.)

arterioles. It is illustrated in figures 65 to 70. The most common form is an apparent thickening of the wall, visible as a thin line on each side of the column of blood (fig. 67). It rarely becomes as heavy as that in figures 65 and 66. Although only one or two venules may be involved, more often

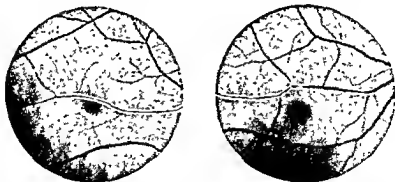


Fig. 66a and b—Two views of the inferior temporal vein of the right eye, showing unusually heavy sheathing. The proximal and peripheral limits of this sheathing are evident, as are also irregularities in its density. (The dark spot below the center of each picture is an artefact.)

several in each eye may be sheathed, and occasionally almost all the veins at the midperiphery are sheathed. Sheathing does not extend closer than about two disk diameters from the optic disk. In some instances, the thickening of the wall intrudes into the lumen (fig. 68), causing local constrictions in the caliber of the blood column. In one case the narrowing

was intense enough to cause engorgement of the branches of the vein beyond the area of constriction. In another case it so constricted a venule as to cause two small hemorrhages in the area drained by the venule. In several instances isolated cuffs of varying density formed around the veins, as in figures 69 and 70.

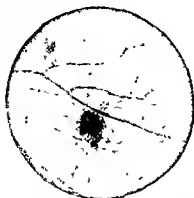


Fig. 67.



Fig. 68.

Fig. 67.—The inferior nasal vein of the right eye is thinly sheathed peripherally, toward the lower right-hand portion of the photograph. This thin type of sheathing is the most common.

Fig. 68.—Irregularity in the caliber of the ascending branches of the left superior temporal vein. The thickening of the walls of the veins seems to have intruded into the lumens of the veins, producing localized narrowings.



Fig. 69.



Fig. 70.

Fig. 69.—Two white plaques overlaid an ascending vein in the left eye.

Fig. 70.—A small cuff encircles a temporal vein in the right eye slightly to the right and below the center of the photograph. Two other cuffs were present in the same eye; at the next examination nine months later all three were gone.

Opacities in the vitreous are associated with the sheathing in 20 per cent of cases. They are never abundant or stringy. Most of them are round and white, and the diameter of a large vein. The majority lie a millimeter or two in front of the retina, generally near the site of a cuffed vein.

The length of time during which the sheathing persists was difficult to determine, because the majority of patients were examined only once.

Repeated examination of thirteen patients was possible and supplied the following information. In six cases negative results of ophthalmoscopic examination had been reported a few months or a few years prior to the finding of the sheathing, proving that the sheath was not a congenital rest. In three of these six cases later observations disclosed that the sheath had disappeared. This group of three is an important one, for in them the sheathing was seen to appear and to disappear. More frequent observations than were possible would have been necessary in order accurately to determine its duration. In one of the cases the sheathing persisted for more than one month and less than one year. In another case it persisted about two years. In the third case observations were so infrequent that it is known only that sheathing persisted at least a few months, and less than sixteen months.

In seven other cases sheathing was found on the first examination and further observation disclosed that it persisted for the following periods: twenty-five months in one case, six months in three cases, three months in one case and two months in two cases.

How much longer than these periods it may have persisted is not known.

From these observations it becomes evident that sheathing of the retinal veins may appear and disappear during the course of multiple sclerosis, and that it persists for periods ranging from several months to two years.

An opportunity to study its structure under the microscope has not yet presented itself.

CLINICAL MATERIAL STUDIED

Since March 1, 1944, and up to December 31, 1946, 103 patients previously unreported on with retinal venous sheathing have been encountered at the Mayo Clinic. All except five of them were examined personally. Of this group of 103 patients, seventy-nine received a diagnosis of multiple sclerosis, eight did not receive such a diagnosis but had signs that made it a possibility, and sixteen presented no history or had no signs that would lead to such a diagnosis.

During the period covered in this study, approximately 1,100 patients admitted to the Mayo Clinic received a diagnosis of multiple sclerosis. The incidence of retinal sheathing hence becomes somewhat more than 100 in 1,100 cases of multiple sclerosis, or roughly 10 per cent, which is the same as that found in the study of an earlier group. Conversely, it might be noted that 90 per cent of the patients afflicted with multiple sclerosis did not present this change in their retinas. In a group of fifty-two patients hospitalized for multiple sclerosis, one of my associates found the incidence of retinal sheathing to be 20 per cent, on diligent search under full mydriasis.

OBSERVATIONS

The ages of the group of 103 patients ranged from sixteen to sixty-one years at the time of examination. The distribution according to age by decades was as follows: less than twenty-one years old, one patient; between twenty-one and thirty years old, twenty-six; between thirty-one and forty years old, thirty-six; between forty-one and fifty years, twenty-seven; between fifty-one and sixty years, twelve patients, and more than sixty years old, one patient.

This distribution of age is similar to that of any average group of persons afflicted with multiple sclerosis.

In the group of seventy-nine patients who received a definite diagnosis of multiple sclerosis the duration of the disease at the time of examination ranged from eight days to thirty-two years. Ten had had symptoms for more than ten years, and eleven had had them for less than one year. The symptoms of the other fifty-eight patients had been present between one year and ten years.

It appears evident that retinal venous sheathing occurs at any age and at any time in the course of the disease.

Nystagmus is an important symptom in multiple sclerosis. It was present at the time of examination in twenty-nine of the seventy-nine patients who had this disease, in four of the eight who might have had it, and in none of the sixteen who did not receive such a diagnosis. This incidence of nystagmus corresponds to that usually found in the presence of this disease.

The cerebrospinal fluid of forty patients was examined. In twenty-one specimens nothing abnormal was found. Among the other nineteen a gold-sol curve characteristic of paresis was reported in ten specimens, five or more cells per cubic millimeter in twelve specimens and protein of 45 mg. or more per 100 c.c. in five. There was some overlapping of these observations in individual cases. All the patients who had abnormal cerebrospinal fluid received a diagnosis of multiple sclerosis. Again, this conforms with the usual experience in multiple sclerosis of the finding of a variation of one sort or another in the cerebrospinal fluid in approximately half the cases.

Retrobulbar neuritis is recognized as an early symptom in multiple sclerosis. In this group of 103 patients it occurred as the first episode in the course of the disease of fifteen patients, and appeared later in six other patients.

Pallor of one or both optic disks was noted in twenty-eight instances.

This detailed review indicates that those patients who have retinal venous sheathing are suffering from no particular form of multiple sclerosis, for their signs and symptoms resemble those of any other group of patients suffering from this disturbance. The sheathing appears at any age and at any time during the course of the disease. There is some reason to suspect that the sheathing may appear with exacerbations, but the proof is not at hand.

It was noted earlier in this thesis that of the entire group of 103 patients, seventy-nine received a definite diagnosis of multiple sclerosis, made after a careful history and examination by competent neurologists.

For eight others such a diagnosis was not made, but these eight patients presented signs or symptoms which were suggestive of this disease, even though they were not convincing enough to lead to a positive diagnosis. Two of these patients had had episodes of acute retrobulbar neuritis followed by spontaneous recovery; two were considered by the neurologist to be too old to have multiple sclerosis and their condition was diagnosed as "degenerative lesions in the central nervous system"; three presented minimal objective signs on neurologic examination; and one failed to exhibit the usual fluctuations in the course of the disease, although the symptoms resembled those of multiple sclerosis in other respects. Whatever it was that afflicted this group of eight patients, it at least resembled multiple sclerosis.

For sixteen other patients the diagnosis of multiple sclerosis likewise was not made, for they presented none of the usual signs or symptoms.

Three of these had syphilis at the time of examination, as evidenced by strongly positive reactions to serologic tests, and may well have had a diffuse, low-grade choroiditis which had caused too little disturbance in the pigment to be apparent to the examiner. One other patient did have old healed choroiditis in one eye. There may have been a milder form of choroiditis in the other eye, even though none was visible, for retinal veins in both eyes were sheathed. Two other patients had suffered injuries to the head in the past, and may have had injury to the eyes, also. One had barely survived eclampsia and toxemia of pregnancy ten years previously. Five others presented an assortment of disturbances of the central nervous system, and the remaining four presented few signs of any sort. In this group of sixteen patients the sheathing of the retinal veins in several instances seems to have been due to a mild inflammatory reaction in the choroid, and a consequent proliferation of glial tissue around the retinal veins. In other instances the sheathing was unexplained.

VALIDITY OF THE CONCEPT OF RETINOPATHY OF MULTIPLE SCLEROSIS

In the light of the data presented previously herein, the question of the validity of a concept of the retinopathy of multiple sclerosis may now be explored. It has been shown that approximately 10 per cent of patients afflicted with multiple sclerosis present, on ophthalmoscopic examination, a visible sheathing of the walls of their retinal veins. (Ninety per cent of such patients do not show this change.) Of the group of 103 patients studied, seventy-nine received a diagnosis of multiple sclerosis and in eight more such a diagnosis was a likely possibility. In the remaining sixteen this diagnosis could not be entertained, and this group represents the errors if venous cuffing is to be considered as a diagnostic sign in multiple sclerosis.

On this basis, it would appear that the finding of retinal venous sheathing of the type described earlier in this paper should suggest the possibility of multiple sclerosis, that it is indicative of this disease in 80 to 85 per cent of the cases, and that in 15 to 20 per cent of the cases it is in error. This error can be reduced by elimination of those cases in which there is even slight evidence of previous inflammatory reaction within the eye and those cases in which syphilis is present.

CONCLUSION

Sheathing of the retinal veins occurring away from the optic disk and without visible cause appears to represent an entity worthy of being regarded as a retinopathy of multiple sclerosis.

THE PRESENT STATUS OF THE FENESTRATION OPERATION FOR THE RESTORATION OF HEARING TO CONVERSATIONAL LEVELS IN LOSS OF HEARING DUE TO CLINICAL OTOSCLEROSIS*

HENRY L. WILLIAMS

It was felt that the fenestration operation would be understood better, if an attempt were made to answer the usual questions that are asked by both the medical profession and the laity in regard to it. The information contained herein is based on the accounts in the literature and the experience gained in performing more than 200 fenestration operations at the Mayo Clinic.

QUESTIONS AND ANSWERS

What Patients May Expect to Have Their Hearing Restored by the Fenestration Operation? A patient whose loss of hearing appears to have been produced by bilateral otosclerosis, may secure permanent restoration of hearing to normal conversational levels but not normal hearing in the ear on which operation is performed. Such a patient will be rehabilitated from the social and economic standpoint.

What Percentage of Patients on Whom Operation Is Performed May Expect to Receive Worth-while Benefit from the Procedure? Lempert, who perfected the fenestration operation, reported that up to the time of his report 33 per cent of patients who had been operated on six years or more before had been rehabilitated socially and economically through restoration of the hearing to normal conversational levels. Through recent improvements in technic he considered that in approximately 70 to 75 per cent of cases primary restoration of the hearing to normal conversational levels could now be secured in the ear on which operation is performed. The fenestra rarely closes if it has remained open for two years. In more than 200 fenestration operations performed at the clinic I have been able to secure good early results in more than 90 per cent of cases but an estimate of the eventual results at this time cannot be made as the first operation was performed only two and a half years ago. In approximately 3 per cent of the cases the ability to hear may be decreased by the operation and in 1 per cent hearing may be seriously impaired.

What Is Otosclerosis? Otosclerosis is a disease in which pathologic changes occur in the otic capsule. Osteoclasts destroy the bone of the otic capsule and the destroyed region is rebuilt in a disorderly manner by osteoblasts. When this process produces ankylosis of the stapediovestibular joint, deafness will result.

Otosclerosis is primarily a disease of bone and stapedial ankylosis is an incidental complication that occurs occasionally. In Guild's study stapedial ankylosis occurred in only ten of eighty-one ears examined in which otosclerosis was present.

"Otosclerosis" is purely a histologic diagnosis and if the diagnosis is made on the living patient the term must be modified to read "clinical otosclerosis." The diagnosis of clinical otosclerosis can be arrived at with reasonable accuracy by excluding, by history and examination, all other

* From the Minnesota State Medical Association Speaker's Library Service: Treatment of hearing loss. 1940, 5 pp.

conditions likely to produce a conduction type of deafness. The diagnosis of clinical otosclerosis, therefore, requires not only careful examination but wide clinical experience.

How Does the Fenestration Operation Improve Hearing? It has been known for many years that in conduction deafness draining off a portion of the perilymph, and thus giving increased mobility to both perilymph and endolymph, would produce immediate marked improvement in the ability to hear which is again lost when the perilymph refills the perilymphatic space. The hypothesis has been presented that in the fenestration operation, by making the tympanic membrane more responsive to vibrations through removal of the head of the malleus and by leaving the tympanic membrane attached to a thin flap of membrane which is used to cover and maintain patent a new opening into the perilymph, a permanent condition is produced in which the endolymph is more mobile and is stimulated by the more vigorous vibrations of a mobilized tympanic membrane. Therefore to secure good results the tympanic membrane must be intact and capable of increased response to sound waves. In conduction deafness secondary to inflammation in the middle ear this condition does not obtain, so chronic adhesive deafness, although of the conduction type, is not likely to be corrected by the fenestration operation. It is apparent that when deafness is produced by atrophy of fibers of the cochlear nerve or of the organ of Corti hearing will not be improved by the fenestration operation, nor will hearing be improved if the deafness is due to immobilization of the tympanic membrane secondary to closure of the eustachian tube.

Can Operation Be Performed in All Cases in Which a Presumptive Diagnosis of Clinical Otosclerosis Can Be Made? In clinical otosclerosis there appears to be an increased number of cases in which atrophy of the fibers of the cochlear nerve or cells of the organ of Corti occurs. It is not known whether this atrophy is one of disuse secondary to immobilization of the endolymph, whether it is produced because fixation of the stapes tends to promote acoustic impairment by abolishing the protective effects of contraction of the stapedius muscle, or whether the degeneration of the nerve is secondary to something inherent in the otosclerotic process itself. Such atrophy is usually termed "secondary nerve degeneration." It is found more frequently and at an earlier age in patients who have clinical otosclerosis than in the general population.

When secondary nerve degeneration occurs with clinical otosclerosis the probability of obtaining a good result from the fenestration operation is diminished. If such degeneration is evidenced only for frequencies higher than those of the range of speech, it will not affect the results to be expected from the operation to a great degree, but if evidence is present that such a change is beginning to affect hearing in the range of speech, chance of success of the operation in restoring hearing is inversely proportional to the degree of degeneration present.

Since acuteness of hearing is inversely proportional to the loudness of sound, measured in decibels, that is necessary before a sound is heard, the ordinary audiometric testing is the reverse of the ordinary intensity level chart measured in decibels. The intensity reference level, 0 decibel, is placed at the top of the audiometric chart and represents the threshold of hearing of the normal ear.

It has been found that the 30 decibel line is the "critical level" for conversational speech. At 5 decibels above this line, an individual will experience little difficulty in understanding speech while at 5 decibels below this line the individual is severely handicapped in understanding conversation. The two most important frequencies for understanding speech are the 1,024 and 2,048 cycles per second. If hearing for sounds in these frequencies is above the 30 decibel line even if the hearing for lower frequencies is below this line, the individual with a loss of hearing may be only slightly handicapped.

It is easy to understand why this small apparent difference in decibels makes so much difference in understanding speech when it is realized that it requires ten times the relative sound energy to produce sounds at 35 decibels as it does at 25 decibels.

Lempert has stated that the average improvement in hearing measured in decibels which is produced by a successful fenestration operation is 20. Since the objective to be attained by the fenestration operation is to improve the hearing to a point above the critical 30 decibel line, it can be readily seen that to restore the hearing of a deafened individual who requires that speech be produced at a loudness of more than 50 decibels before it can be understood, would require a better than average response to the operation. Therefore an individual who has a loss of hearing of 50 decibels or more must expect much less than the average chance (as estimated on the basis of the so-called ideal case) of getting a successful primary result from the operation. Most surgeons using this procedure estimate that primary restoration of hearing to above the 30 decibel level can be obtained in from 70 to 75 per cent of all "ideal" cases in which operation is performed. In a further 20 to 25 per cent, improvement somewhat less than to the desired level may be secured.

It can be readily seen that in a patient who has otosclerosis, loss of hearing to the 30 decibel line or more and in addition evidence of secondary nerve degeneration, the probability of securing a primary good result is slight. From this information it should be possible to estimate whether or not the chance of success from this procedure in a certain case is sufficient to warrant the patient's submitting himself to the operation.

It is the increasing tendency toward degeneration of the auditory nerve, not age, that usually makes the fenestration operation unsuitable for patients who are more than fifty years of age.

In Cases in Which the Results Obtained from the Fenestration Operation Are Not Good What Is the Usual Cause of Failure? The patients who do not obtain good results from the operation may be divided into four groups: The first group is composed of that 3 per cent of patients in whom the hearing is made worse by operation. The remainder can be almost equally divided into three groups: a group in which patients receive some improvement in the hearing but the improvement does not reach the level at which normal conversation can be heard; a group in which the hearing is not affected either for better or for worse by the operation, and a group in which, after an initial improvement in hearing, it returns to the preoperative level as a result of the closure of the fenestra by formation of new bone. In this last group a second operation, in which the flap over the fenestra is elevated and the fenestra reopened, offers promise of more permanent

restoration of hearing as the tendency toward regeneration of bone tends to become exhausted.

If Operation Is Unsuccessful Will It Be Impossible for the Patient to Use a Hearing Aid? As good hearing can be obtained with a hearing aid after the operation as before because the ear in which hearing is poorer is nearly always selected for the operation and the hearing of the other ear will not be impaired. A hearing aid may be successfully fitted to the surgically treated ear after healing has taken place except in the 3 per cent of cases mentioned previously.

Would a Patient with Otosclerosis Be Better Off If He Purchased an Electric Hearing Aid Rather Than Submit to Fenestration? There is in reality little conflict between the hearing aid and the fenestration operation in attempts to restore hearing to the deafened. At the Mayo Clinic we do not find that more than 50 per cent of the patients presenting themselves as candidates for this procedure are found to meet the criteria which we have set up as qualifying a patient to undergo this procedure.

In the study of serially sectioned temporal bones secured at random, Guild stated that without exception the material on which his report is based is in agreement with opinion that otosclerosis does not cause an impairment of hearing until or unless a bony connection becomes formed between some part of the margin of the oval window and the stapedial footplate. The stapediovestibular articulation had become ankylosed in only ten of the eighty-one ears in which there was histologic otosclerosis. In the region of the oval window in the sixty-five ears studied the otosclerotic process was active in thirty-two ears and quiescent in thirty-three ears but in all the cases in which stapedial ankylosis had occurred the otosclerotic process was of good size and active. In none of the cases in which otosclerotic processes involved the region of the round window, even though the round window appeared to be almost completely closed, had the disease progressed to the point at which hearing was affected.

This material enables one to answer three questions in regard to the advisability of the fenestration operation in cases of loss of hearing presumably secondary to ankylosis of the stapediovestibular articulation. 1. Is the involvement of the round window likely to make a good result from the fenestration operation impossible? 2. Is progression of the otosclerotic process likely to compromise the organ of Corti and so vitiate the result obtained by fenestration? 3. In a case of clinical otosclerosis is quiescence of the process probable before such serious impairment of the hearing takes place that it will be difficult to obtain adequate restoration with an electric hearing aid? From the material presented it seems logical to conclude that these questions should be answered in the negative.

I feel therefore that a patient with an early otosclerosis is justified in submitting himself to the fenestration operation because if the operation is a success he will be spared the expense of purchase and maintenance of an electric ear phone which in a few years will amount to more than the cost of the fenestration operation. Holmgren observed in his series of thirty-four fenestrations reported in 1937 that in many patients in whom the operation had seemed to be a failure, the hearing in the ear on which the operation had not been performed became progressively worse but in the ear on which operation had been performed the hearing remained stationary.

Even though Holmgren selected the worse of the two ears to be operated on, after several years the ear on which operation had been performed became the better in nearly all instances.

Since in all instances the patient can secure as good hearing with a hearing aid subsequent to the operation as before, the tendency of the operative procedure to terminate progress in the hearing loss makes the procedure in my opinion a worth-while gamble.

What Information Is Given to Patients Who Inquire about the Feasibility of the Fenestration Procedure? If the patients who inquire are found to have clinical otosclerosis of an operable type each is informed of the possibility of obtaining a good result for his particular condition. It is pointed out that this procedure is optional and carries a definite risk. They are told that they must weigh this risk against the results to be obtained by use of a hearing aid with which no risk is present. If the patient appears to appreciate fully the advantages and disadvantages of the procedure and wishes to have it carried out we in the Section on Otolaryngology feel justified in performing the operation.

SUMMARY

To sum up, the fenestration operation may be properly done in a case of progressive conduction deafness which exhibits little or no evidence of degeneration of cells or fibers of the organ of Corti and which does not appear to be on an inflammatory basis, providing the patient understands the percentage probabilities both of restoration of hearing and of failure to restore hearing and also the possibility of increased loss of hearing in the ear on which the operation is performed. Except for the small chance of worsening the hearing by the fenestration operation the patient has lost little by the operation even if it is unsuccessful.

As Holmgren pointed out even an unsuccessful operation tends to stop the progress of the hearing loss in the ear operated on. Even if the most conservative estimate of good results to be found in the literature, which is Lempert's estimate of 33 per cent, continued restoration to conversational hearing among patients on whom the operation was performed six years or more previously is taken as the best obtainable result, the procedure seems well worth while. It can be compared favorably in its results to those obtainable by the operation for detached retina.

Many surgeons have given more encouraging reports than this but no other surgeon than Lempert can report a series of six year cures.

With the advance in the technic and good end results that will take place with so many otologists working on the problem, I think that we can feel sure that the fenestration procedure has gained a permanent position in otologic surgery.

FOREIGN BODIES IN THE EXTERNAL AUDITORY CANAL CAUSING OTITIS MEDIA*

KINSEY M. SIMONTON

Foreign bodies impacted in the external auditory canal or middle ear may be of serious importance. Any object small enough to enter the external auditory canal is a potential foreign body in this location. Foreign bodies enter the external auditory canal by act of the person concerned, by carelessness and by accident. Small objects such as seeds, beads, rubber erasers from pencils, steel springs, balls of paper or stones may be placed in the ear by children at play. Adult persons in misguided therapeutic efforts scratch the external auditory canal with match sticks, toothpicks and hairpins. Cotton pledgets and gauze wicks placed in the external auditory canal by patient or physician may be forgotten and left in the canal, as may rubber ear plugs used by swimmers. One patient has been seen at the Mayo Clinic in whom a cast of plaster of Paris became lodged against the tympanic membrane while an impression was being made for the ear piece of a hearing aid. Flying insects are the most frequent of the foreign bodies which enter the ear by accident. Workmen are subject to having flying bits of plaster, drops of paint, wood chips or small stones enter the ear. Gasoline or oil may enter the ears of automobile mechanics. Bits of straw and the seeds of foxtail grass are found in the ears of farmers. Cerumen, when it becomes dry and hard, acts as a foreign body.

The tympanic membrane is damaged by relatively few of the foreign bodies which enter the external auditory canal. Injury to the tympanic membrane results from (1) direct trauma by the entering foreign body, (2) caustic or irritating action of the foreign matter, (3) prolonged contact of the foreign body with the ear drum, and (4) trauma incurred during attempts at removal of the foreign body.

DIRECT TRAUMA

Perforation of the tympanic membrane by direct trauma inflicted by the entering foreign body occurs occasionally when the external auditory canal is scratched with a match stick or similar object which is inserted too far into the canal. The extreme sensitivity of the external auditory canal is nature's best protection against this accident. The sharp pain incident to perforation of the tympanic membrane causes immediate removal of the foreign body. Inflammation resulting from this accident usually is slight, and is confined principally to the ear drum. Healing by first intention generally occurs without significant sequelae. The anatomic curvature of the external auditory canal protects the tympanic membrane from injury by flying foreign bodies unless the foreign body enters the canal with extreme force.

CAUSTIC ACTION

Destruction of the tympanic membrane by the caustic action of foreign matter in the external auditory canal causes severe damage to the structures of the tympanic cavity. Two cases will illustrate this point.

* Submitted to the Archives of Otolaryngology.

A man complained of bilateral loss of hearing. He stated that he had placed a solution of phenol in each external auditory canal in order to escape duty with the German Army in World War I. Examination revealed complete destruction of the tympanic membrane and other structures of the middle ear. The tympanic cavities were lined with dense, glistening scar tissue. Severe deafness of the conduction type was noted in each ear.

A man stated that sludge from the bottom of an automobile gasoline tank had entered his left ear six years previously. He had suffered immediate severe pain, followed by continuous drainage of foul pus from the ear and occasional headache and vertigo. Examination revealed severe deafness of the conduction type. A large polyp, which arose from a perforation in the posterosuperior portion of the tympanic membrane, filled the external auditory canal. Roentgenograms were interpreted as showing the cavity of a cholesteatoma. Radical mastoidectomy was performed. A large cholesteatoma cavity was found which exposed the dura in the temporal fossa. The middle ear was filled with granulations; the ossicles were necrotic.

Gasoline which enters the external auditory canal causes severe pain. If the patient heeds this warning and has the gasoline removed within a few minutes, damage is limited to acute inflammation of the ear drum and canal. Prolonged exposure to the irritant may cause necrosis of the ear drum.

PROLONGED CONTACT

Most foreign bodies cause irritation and pain. This is fortunate in that the patient seeks the assistance of a physician, so that the foreign body is removed before the inflammatory reaction becomes advanced. Living foreign bodies (insects) cause marked irritation by their movements, and are removed early. Inanimate foreign bodies cause irritation by pressure. However, foreign bodies sometimes are found which obviously have been in the external auditory canal for a long period, the patient having been unaware of them. Cotton pledgets and small rolls of paper frequently cause no irritation. Infection of secretions which are retained in the external auditory canal by the foreign body causes otitis externa and myringitis, and may cause perforation of the tympanic membrane by ulceration. Tightly lodged foreign bodies may prevent escape of secretions and desquamated epithelium, and lead to the formation of cholesteatoma in the external auditory canal. This is illustrated by solid masses of cerumen covered by concentric layers of desquamated epithelium which cause necrosis of the tympanic membrane and tympanic ring to form the so-called natural radical mastoid cavity. The following cases illustrate damage to the tympanic cavity by various retained foreign bodies.

A soldier was admitted to a military hospital complaining of unilateral loss of hearing. Examination revealed a tightly impacted mass of cerumen which resisted removal by irrigation and curet. With the patient under the influence of general anesthesia, the mass was removed. It was surrounded by concentric layers of cholesteatoma which had destroyed the tympanic membrane and the ossicles, and had eroded widely into the periantral region of the mastoid process. The facial nerve was exposed in the cavity, and was injured during removal of the mass.

A boy seven years old complained of pain in the left ear of twenty-four hours' duration. A watermelon seed, which apparently had been in the external auditory canal for a prolonged period, was removed. The canal was inflamed, but the tympanic membrane was normal at the time the seed was removed. On the next day a bleb was noted on the tympanic membrane, and was incised. Pain persisted and was accompanied by the gradual development of myringitis and otitis media. Recovery occurred after myringotomy was done.

A boy eight years old complained of fever and of pain in the right ear of twenty-four hours' duration. A kernel of corn was removed from the right external auditory canal. A perforation was present in the tympanic membrane, which was inflamed. Drainage from the middle ear persisted for two weeks, at the end of which the perforation healed.

A man sixty-one years old complained of itching and swelling of the ears of fifteen years' duration. He said that the right ear drum was absent. He had undergone much treatment without relief, and often had scratched the external auditory canals with cotton until bleeding occurred. Examination revealed marked thickening of the skin of the auricles, conchae and canals of both ears. The external auditory canals were narrow. Foul-smelling pus was present in the right external auditory canal; epithelial debris was present in the left. At the initial examination a broken piece of toothpick was removed from the right external auditory canal. Treatment by dressings kept wet with solutions of penicillin, sodium aspergillate and aluminum acetate did not produce improvement in the right ear. Radical mastoidectomy was performed on the right. Chronic inflammation of the mastoid cells was found. A piece of string, 1½ inches long, was removed from the tympanic cavity. The patient had not been aware of the presence of either foreign body.

After the operation a cotton wick was placed in the patient's left external auditory canal. The patient returned later in the day complaining of sudden loss of hearing. The cotton wick had been pressed tightly against the drum, medial to the isthmus.

TRAUMA INCIDENT TO REMOVAL

Foreign bodies which become lodged in the bony portion of the external auditory canal medial to the isthmus lie near or against the tympanic membrane. Removal should be achieved by irrigation if possible, or manipulation should be carried out with the utmost care. If the foreign body is tightly lodged, the difficulty of removal is increased by swelling of the wall of the canal due to inflammation or to trauma from attempted removal. General anesthesia should be employed for the removal of tightly lodged foreign bodies. In some cases it is best to approach the foreign body through the mastoid process to avoid damage to the tympanic membrane.

A boy seven years old was brought to the clinic because of a bead in the left ear which had been present twenty-four hours. A similar bead had been removed from the right ear. Attempts to remove the bead through the external auditory canal and through a postauricular incision had been unsuccessful. A probe had been broken off in these attempts, and the tip of the probe remained in the left ear. Examination revealed a recent postauricular incision on the left. The external auditory canal was large, with little inflammatory reaction. Roentgenograms revealed a bead in the left external auditory canal, medial to the isthmus. A small bit of metal lay below the bead.

With the patient under the influence of general anesthesia, the bead was manipulated, engaged with forceps, and removed through the external auditory canal. A small bit of metal, the tip of the probe, was found embedded in granulations in the region of the eustachian tube. The malleus was clearly visible after removal of the foreign body, indicating destruction of the tympanic membrane. Because of loss of epithelium from the wall of the external auditory canal at the isthmus, a rubber tube was left in the canal to prevent atresia. The patient was able to hear a low conversational voice in the left ear after removal of the foreign body.

SUMMARY AND CONCLUSIONS

Foreign bodies in the external auditory canal occasionally cause damage to the tympanic membrane and tympanic cavity. The patient may not be aware of the presence of the foreign body. Early removal of foreign bodies is advised, especially when they are substances which cause necrosis of tissues. Great care is necessary to avoid injury to the tympanic membrane during manipulation of the foreign body. The use of general anesthesia is advisable during removal of lodged foreign bodies.

RECENT ADVANCES IN THE MANAGEMENT OF EAR,
NOSE AND THROAT PROBLEMS*

OLAV E. HALLBERG

INFECTIONS OF THE MIDDLE EAR

Hadjopoulos and Bell stated that there are two types of infections of the middle ear. One of them is caused by an obligate aerobe, and produces an infection limited by the amount of oxygen present in the spaces of the middle ear when inflammatory swelling closes the eustachian tube. Such an infection often is characterized by a violent onset of pain in the affected ear. Spontaneous rupture or myringotomy results in almost immediate subsidence of symptoms, and the secretions dry up within a few days without any treatment.

Probably, however, in the majority of cases, the infection is of the second type; that is, it arises by invasion of a facultative anaerobe which might reach the middle ear and mastoid process either directly through the tube or along the submucosal lymphatic vessels of the eustachian tube. This type of organism is able to multiply in the presence of a very low oxygen tension, and it produces a more dangerous infection of the middle ear and mastoid process than might otherwise occur. At the onset, there might be marked tenderness over the mastoid. If it looks as if mastoiditis might develop, both sulfonamide compounds and penicillin should be administered immediately. The medication should be continued for several days after the discharge has stopped. As you know, during the past several years there has been no severe mastoid disease, and the tendency is to give the sulfonamide drugs and penicillin all the credit for this situation. We know, however, that streptococci and pneumococci may vary in virulence from year to year.

At the Mayo Clinic we have lately seen several patients with surgical mastoiditis arising from influenza and measles contracted during a local epidemic. The mastoiditis in these cases became so severe as to require surgical treatment in spite of adequate sulfonamide and penicillin therapy that had been instituted at the very onset of the infection. So far as biologic resistance is concerned, it is now an established fact that immunity to infection does not develop when the infection is terminated by chemotherapy or antibiotic agents. I am sure we all have experienced this sad fact. It is especially annoying when it occurs among babies with infections of the upper part of the respiratory tract. As soon as one infection has been terminated by these means, another one starts right away.

I should like to make a plea that you do not consider your patient all but cured after you have started to administer chemotherapy and antibiotics. At the Mayo Clinic, we feel that we have encountered more patients with serious mastoiditis and complications than previously. Many of these patients had been receiving adequate sulfonamide therapy and then began to receive penicillin. The "masking" effect of these drugs is an important thing to recognize.

Otitic meningitis is caused by either acute or chronic infections in the middle ear or mastoid process. Before the advent of chemotherapy this

* Abridgment of paper published in full in *Minnesota Medicine*, 30: 1135-1160 (Nov.) 1947.

disease had a very poor prognosis. Now the chance of cure is almost 100 per cent if the treatment is not started too late. Septicemia caused by infection of the ear or its complication, thrombophlebitis of the sigmoid sinuses, now can be attacked successfully by combined chemotherapy and surgery. Abscess of the brain secondary to disease of the ear also has a better prognosis than formerly.

MÉNIÈRE'S DISEASE

Ménière's disease probably has an allergic background. The reaction is not of the antigen-antibody type; the condition might belong in a group of the so-called physical allergies which is intimately connected with disturbed permeability of cell membranes and disturbed electrolytic metabolism.

Histamine is still used in the treatment of Ménière's disease. Horton treated 270 patients with histamine (1 grain or 0.065 gm. of histamine base in 250 to 500 c.c. of isotonic solution of sodium chloride). Seventy per cent obtained complete remission, with improvement of hearing in 40 per cent. Many of these patients suffered remissions when treatment was discontinued in a month to a year. Lately, at the clinic, we have used a combination of nicotinic acid and potassium nitrate, with good effects. All treatments aim at control of fluid metabolism, correction of balance in the tissue fluids and production of vigorous vasodilatation.

When medical management does not control the dizziness, surgical treatment can be attempted. For a long time, only section of the eighth cranial nerve was done. In this type of surgery there is always a certain risk, since the surgeon must proceed intracranially in order to reach the nerve. Lately, transmastoid labyrinthotomy has come into favor.

In the selection of patients for surgery only those whose hearing in the diseased ear is not useful should be chosen, since in our cases the hearing disappeared entirely in the operated ear. Patients who have almost normal or fairly normal hearing should have the benefits of long and fair trial of conservative measures. The operation itself is fairly simple. We use a postauricular incision. As much of the mastoid process is exenterated as is possible, so as to provide enough operative room. The horizontal semicircular canal is exposed to view all the way anteriorly to the junction with the anterior vertical canal. With an electrically driven burr, a small hole is made in the horizontal canal about 2 mm. posterior to the ampulla. A thin, curved electrode is inserted into the vestibule and light cautery is used. Transitory facial palsy often develops among these patients. It disappears within two weeks to a month. Penicillin is used during convalescence to prevent infection.

OTOSCLEROSIS

The greatest advance in the treatment of a certain type of deafness is the fenestration operation for otosclerosis. This operation is indicated only in certain selected cases of otosclerosis in which bone conduction is good and in which there is little if any damage to the acoustic nerve. The diagnosis of otosclerosis has to be made by exclusion. The onset of loss of hearing usually is very insidious; most often hearing begins to diminish when the patient is between ten and twenty years old. These patients often hear better in noisy places. A familial history of deafness can be obtained in

about 10 per cent of cases. Otosclerosis is a disease in which pathologic changes occur in the auditory capsule. Osteoclasts destroy the bone of the auditory capsule and the destroyed region is rebuilt in a disorderly manner by osteoblasts. When this process causes ankylosis of the stapediovestibular joint, deafness will result. Otosclerosis is primarily a disease of bone, and stapedial ankylosis is an incidental complication that occurs occasionally. In a study of the temporal bone, it was found that stapedial ankylosis occurred in only ten of eighty-one ears examined in which otosclerosis was present. Otosclerosis is only a histologic diagnosis, and if the diagnosis is to be made for the living patient, the term must be modified to "clinical otosclerosis." The diagnosis of clinical otosclerosis can be arrived at with reasonable accuracy by exclusion, on the basis of the history and results of examination, of all other conditions likely to produce a conduction type of deafness.

The fenestration operation is applicable only to patients who have clinical otosclerosis and in whom the hearing reserve is so great that release of it will rehabilitate the patient socially. In 317 fenestration operations performed at the Mayo Clinic, we have been able to secure good early results in about 90 per cent of the cases. It would seem that about 70 per cent of the patients will have permanent good results, although it is still a little too early to be certain, because we started to employ this type of surgery only about two and a half years ago. In approximately 3 per cent of the cases the ability to hear may be decreased by the operation, and in about 1 per cent complete deafness may develop in the operated ear. The latter result, we feel, is caused mostly by hemorrhage into the labyrinth or by an infection.

What are the usual causes for failure? I shall only enumerate them: (1) faulty diagnosis, (2) osteoma (I have seen two patients with such lesions), (3) closure of window with regeneration of bone, in which event the surgeon must be very careful so that all bone chips are removed from the window, (4) infection with development of labyrinthitis, (5) late infection with fibrosis of the endolymphatic duct, (6) hemorrhage into the labyrinth after surgery, and (7) poor surgery.

If the patient who seeks aid is found to have clinical otosclerosis of an operable type, he is first informed as to the possibility of obtaining a good result for his particular condition. We tell him that surgery is optional and that it is accompanied by a risk which, however, is small. The patient must weigh this risk against the results obtained by use of a hearing aid, which instruments nowadays are efficient and give promise of even further improvement.

CONDITIONS OF THE NOSE AND THROAT

About fifteen or twenty years ago surgical treatment for a variety of nasal conditions was radical; almost everything that protruded was excised from the nose and the end result for the patient would be a so-called lead-pipe nose. Modern surgical treatment generally has been directed toward retention of the normal physiology of the nose. Penicillin did much to better the therapy of diseases of the nose and throat. The sulfonamide drugs, however, did not prove to be so effective as was hoped in the treatment of infections of the paranasal sinuses.

Röntgen therapy reduces pain promptly, probably by rendering secretions more liquid. Occasionally, roentgen therapy shrinks the mucous membrane sufficiently so that when the next infection occurs there is either no pain at all or it is very slight.

In the treatment of chronic sinusitis much can be done with conservative surgical treatment with penicillin as an adjunct. Penicillin alone will not cure chronic disease of the sinuses. If penicillin is administered the condition of the nose often will improve, but as soon as the use of penicillin is stopped, the infection will recur.

In the treatment of chronic pansinusitis without bronchiectasis, surgery and penicillin are the agents of choice. The treatment of chronic pansinusitis with bronchiectasis is somewhat different: often by the clearing up or amelioration of the condition in the lungs first, remarkable improvement is seen in the nose, and occasionally no further treatment need be directed to the nose. Sometimes the infection extends into the bone, in which instance osteomyelitis arises. The so-called spreading type of osteomyelitis has been dreaded by otolaryngologists. This type of infection occasionally starts after an intranasal operation. These infections usually are caused by an anaerobic streptococcus, and in spite of everything that could be done—that is, before the advent of penicillin—the mortality rate was almost 100 per cent.

Nasal allergy includes seasonal hay fever and so-called vasomotor rhinitis, which is characterized by sneezing and watery discharge in the morning. Of the newer treatments, I should mention that involving histamine. The physiologic effects of histamine are known to be: (1) contraction of smooth muscle, (2) constriction of arterioles, (3) dilatation and increased permeability of the capillaries, with localized edema, and (4) increased secretion by the secretory glands. Because there is a similarity between the action of allergy and that of histamine, small doses of histamine are administered in an attempt to desensitize the patient. Histamine and nicotinic acid can be tried, but in my experience, especially in respect to nicotinic acid, the results have been rather disappointing.

Benadryl (beta-dimethylaminoethyl benzhydrol ether hydrochloride), which is an antihistaminic substance, has been tried much lately. In vasomotor rhinitis it helps only in about 20 per cent of the cases. Moreover, the side effects—drowsiness and nervousness—are most annoying.

A newer drug, pyribenzamine hydrochloride (N,N-dimethyl-N'-benzyl-N'-(α -pyridyl) ethylenedianine hydrochloride), seems to affect vasomotor rhinitis more satisfactorily; 50 to 60 per cent of patients derive benefit from this drug. The side reactions are not so noticeable as are the side effects of benadryl.

Of the newer treatments, I might also mention that involving the use of streptomycin—the newest of the antibiotic agents. Since *Klebsiella ozaenae*, a bacterium which is sensitive to streptomycin, often is found in *ozena*, treatment of this disease with streptomycin has been tried. These experiments were started only recently by Dr. K. M. Simonton, and it is still too early to be able to say whether the patients have derived lasting benefit from it.

Finally, I shall mention the use and misuse of nasal vasoconstrictors. These points recently were stressed by Lake. For a long time it has been

comforters should be discarded. Woolen bedclothes devoid of lint may be used and a generous fold of sheet should be placed over the upper portion of the blankets. Changing and storage of clothing should be done outside this room. Small animals should be kept from the room. Steam or hot-water heat is preferable to hot-air heat. If hot-air vents are in the room, filters of dust-proof fabrics should be provided for these. This room should be cleaned daily with a damp cloth rather than by sweeping or by a dust mop. Should the patient be a child, it is unwise to allow the use of stuffed or fur-trimmed toys.

When the avoidance of contact with an offending inhalant allergen is impossible, the advisability of specific desensitization should be considered. Results from desensitization are less favorable than one might wish. When results are good, the benefit sustained is frequently transient. Scrupulous avoidance of offending allergens remains the most effective form of therapy.

With regard to ingestion of allergens, it is possible that the conscientious patient may place too much emphasis on the problem since it is uncommon for food to be of major importance in the etiology of vasomotor rhinitis which begins after the fourth decade of life. In use of diets designed to exclude offending foods, it must be remembered that no diet should allow the patient's nutrition to suffer. Brief trial periods of no greater duration than one month usually suffice to answer a physician's question concerning the role of ingested allergens. The occurrence of a positive reaction to a skin test is in itself insufficient evidence to omit from a diet nutritious foods known clinically to be tolerated. Through use of bizarre and inadequate diets many patients will cause their health to suffer more than it would from the atopic disorders prompting the use of such diets.

PHYSICAL ALLERGIC FACTORS

The role of "physical allergy," which usually means hypersensitivity of the patient to changes in temperature and the cooling effect of moving air, recently has been emphasized in vasomotor rhinitis.

Patients who have physical allergy can be classed into two groups. The larger group consists of patients whose nasal responses are exaggerated to the usual changes in temperature which are well tolerated by most normal individuals. The smaller group is comprised of persons who are affected by wide variations of temperature or excessive movement of air encountered in their occupations. In this group are included butchers, florists, dairy workers, grocers, gas station attendants and others whose activities or occupations necessitate their frequent entrance into iceboxes, refrigerated rooms or frequent passage in and out of doors. In such patients the nasal reflex responses may be normal to the usual stimuli but are exaggerated to occupational stimuli of greater degree.

Patients in both groups should strive to live in a constant environmental temperature in an atmosphere which is devoid of drafts. Rooms should be adequately humidified and heated without excessive movement of air from ventilating systems. At night the windows should be kept closed in order that the temperature may be maintained at 65° F. or more. The bed, chairs, desks and parts of the house frequented by the patient should be arranged so that he can avoid cross ventilation. Care should be exercised to minimize as much as possible the necessity for entering air-conditioned

huddings and theaters. Adequately warm dress should be encouraged. Minor changes in routine followed in the course of an occupation may greatly lessen contact with the objectionable factors listed.

NEUROGENIC FACTOR

The neurogenic factor is a major contributing cause in the production of nasal symptoms of many patients. The responses observed in vasomotor rhinitis result from a reflex mechanism, and their severity may be appreciably altered by the emotional state. Therapy directed toward the correction of any underlying nervous tension frequently will decrease the severity of nasal symptoms.

ENDOCRINE FACTORS

Nasal changes characteristic of vasomotor rhinitis are observed in the course of certain endocrine disturbances. Lillie and Haines called attention to such a disturbance among patients who have excessively low metabolic rates but do not have myxedema. An elevation of the metabolic rate in such cases is often associated with a regression of nasal symptoms. Vasomotor rhinitis likewise is at times a troublesome complication of pregnancy. Termination of the pregnancy through parturition often brings remission of the symptoms. Women experiencing vasomotor instability associated with the menopause will at times find a paroxysm of vasomotor rhinitis beginning with the flushes. Treatment with estrogenic substances is of value in such instances.

CHRONIC NASAL IRRITATION

Even in the absence of definite evidence of sensitivity patients who have vasomotor rhinitis should exercise every precaution to avoid contact with physically irritating substances which might further aggravate their nasal condition. The use of a dust-free bedroom, the disposal of rug pads, and adequate slip covering or disposal of overstuffed furniture will serve to minimize common sources of nasal irritation. Habits of sniffing, hard blowing, hacking and other objectionable practices into which the victim of vasomotor rhinitis may fall should be discouraged. Tobacco smoke, occupational fumes and contact with heavily scented objects frequently will initiate a paroxysm of nasal congestion or sneezing. To be discouraged is the practice of self-medication by nose drops, sprays and irrigations.

The drainage of secretions from the paranasal sinuses is impaired by mucosal edema during a paroxysm of vasomotor rhinitis. Polypoid degeneration of the nasal mucous membrane likewise will disturb adequate drainage of the sinuses thus tending to bring about a chronic infection in these chambers. Conversely, the constant seepage of irritating and infectious exudates serves to perpetuate the changes noted in vasomotor rhinitis. Should other measures in the management of vasomotor rhinitis fail to bring about regression in the size of polypoid tissue and fail to produce sufficient drainage to allow subsidence of chronic sinusitis, intranasal surgical procedures may be warranted. The use of radium to effect a sub-epithelial fibrosis after polypectomy helps to prevent recurrence of the polyps. Radium applied to lymphoid structures in the nasopharynx is at times valuable in securing adequate drainage from the paranasal sinuses.

A transient type of vasomotor rhinitis at times is observed for days to weeks after upper respiratory infections.

INTRANASAL ABNORMALITIES

A widely deflected nasal septum, nasal spur or markedly hypertrophied nasal turbinates through contact with other intranasal structures may reflexly initiate changes in the nasal mucous membrane which are characteristic of vasomotor rhinitis. The surgical correction of such structural abnormalities in the treatment of vasomotor rhinitis should be deferred until more conservative methods of therapy have proved ineffectual.

COMPLICATIONS

In addition to the polypoid degeneration and chronic inflammatory changes so often observed consequent to vasomotor rhinitis there is a third complication, the vasodilating pain syndrome. Often patients who have this complication complain bitterly of discomfort in the region of the nasal accessory sinuses but no active inflammatory changes are evident within the sinuses. At times fatigue or tension serves to aggravate the severity of symptoms of "stiffness" or "fullness" which occur in the course of vasomotor rhinitis. When pain about the face is the presenting symptom, care should be exercised to exclude an underlying though minimal vasomotor rhinitis as an etiologic factor.

SPECIFIC TREATMENT

The recent advent of drugs manifesting antihistaminic properties represents an advance in the treatment of vasomotor rhinitis. The use of β -dimethylaminoethyl benzhydryl ether hydrochloride (benadryl) and N,N-dimethyl-N'-benzyl-N'-(α -pyridyl) ethylenediamine monohydrochloride (pyribenzamine hydrochloride or tripeleminamine hydrochloride) is of value in these nasal allergic disorders. Using the latter drug Feinberg found that 64 per cent of patients with vasomotor rhinitis were helped. The usual dosage employed in treatment of vasomotor rhinitis with either benadryl or pyribenzamine is 150 to 200 mg. daily in three or four divided doses. The drug is preferably administered after meals and at bedtime.

The use of nicotinic acid is helpful in cases in which the "physical allergy" component is of greatest importance. It is of value because of its vasodilating properties and not because of its relationship to the vitamin B complex. It is good practice to administer nicotinic acid as follows: Injections are administered subcutaneously in daily doses beginning with 25 mg. These are increased by increments of 25 mg. daily to tolerance or until a dose of 100 mg. is attained. Subcutaneous injections of 100 mg. are continued daily for one month. If improvement takes place an additional two months of parenteral therapy is advisable after which nicotinic acid may be given by mouth instead of parenterally. When the drug is given by mouth the dose tolerated is usually from 150 to 200 mg. daily in divided doses.

Histamine therapy has on occasions proved useful in a few cases of vasomotor rhinitis.

Cauterization of the nasal mucous membrane in the region overlying the sphenopalatine ganglion with a 50 per cent aqueous solution of silver

nitrate will at times give temporary relief. This had best be done by one well acquainted with intranasal procedures in the therapy of nose and throat diseases.

Iodides administered orally in the form of the potassium or sodium salt remain especially valuable in the care of patients whose primary complaints are referable to inspissated mucus in the nasopharynx and on the posterior pharyngeal wall. Such mucus is thinned, a procedure which relieves the nasal irritation associated with such dried secretions. In hypersensitive individuals, having an unwarranted fixation of their attention on their nasal functions, such treatment is especially helpful.

CICATRICAL STENOSIS OF THE NASOPHARYNX: CORRECTION BY MEANS OF A SKIN GRAFT*

FREDERICK A. FIGI

Thirty-seven cases of cicatricial stenosis of the nasopharynx have been encountered at the Mayo Clinic. Many authors have stated that syphilis is the most common cause of cicatricial stenosis of the nasopharynx. This is decidedly in contrast to the findings in the cases observed by us at the clinic. Excessive trauma inflicted during tonsillectomy alone or combined with adenoidectomy induced the stenosis in twenty (54 per cent) of the thirty-seven cases. Syphilis was causative in eight (21 per cent) cases, an indeterminate inflammatory process in three, rhinoscleroma in two, a caustic burn with sulfuric acid in one, diphtheria in one, lupus in one and an attempt at surgical correction of a congenital malformation of the throat in one. The duration of the stenosis at the time these patients came for consideration varied greatly. Narrowing of the nasopharynx in these cases may range from slight asymptomatic contracture to complete closure. The symptoms of stenosis of the nasopharynx are essentially those of nasal obstruction and commonly are referred to the accessory sinuses and to the ears. They are dependent to a great extent on the degree of stenosis.

Attempts have been made repeatedly to reline the nasopharyngeal lumen by means of a skin graft but usually these have failed because the graft was inadequately immobilized. In the following case an acrylic obturator was used and an excellent result was secured.

The patient, a housewife, aged fifty years, came to the clinic for treatment on September 16, 1946, because of nasal obstruction of eleven years' duration. She had undergone tonsillectomy in 1932 and the wound failed to heal. At that time results of serologic tests for syphilis were positive.

Examination of the patient at the clinic revealed dense cicatricial atresia of the nasopharynx, complete destruction of the uvula and extensive scarring of the entire posterior and lateral walls of the pharynx (fig. 71). No other clinical signs of syphilis were observed. On serologic examination reaction to the Kline test was doubtful, results of the Kahn test were negative, and results of the Hinton and Kolmer tests were positive. Examination of the cerebrospinal fluid gave completely negative results.

* Abridgment of paper published in full in *Plastic and Reconstructive Surgery*, 2:97-104 (Mar.) 1947.

Antisypilitic treatment with penicillin was begun and five days later surgical correction of the atresia of the nasopharynx was undertaken. Local anesthesia was used. The tip of a heavy curved probe inserted through either nostril into the nasopharynx was barely palpable through the densely scarred palate but it was possible, by use of the probe, to determine the approximate level of the reflection of the mucous membrane on the posterior wall of the nasopharynx and the superior surface of the soft palate. A transverse incision, approximately 4 cm. in length, was made across the posterior wall of the pharynx below the lower border of the scarred attachment of the soft palate to the posterior wall of the oropharynx. This was carried entirely through the thickness of the scarring and was then extended upward in order to free the palate widely from its attachment to the posterior pharyngeal wall. The opening thus created was enlarged sufficiently to permit inversion of the index finger through it into both choanae. A sponge rubber mold through which two rubber tubes had been inserted for nasal breathing was then covered with a split-skin graft of medium thickness. The graft had previously been taken from the anterior abdominal wall. This graft was drawn up into the restored nasopharyngeal

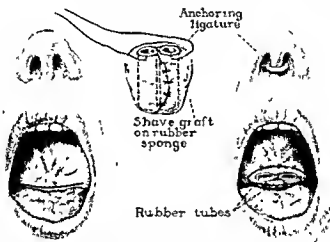


Fig 71.—Drawing on the left shows cicatricial atresia of the nasopharynx due to syphilis. Note transverse incision for re-opening the lumen. Center drawing shows the self-retaining sponge rubber mold with tubes for breathing and silk suture for supplementary anchorage below the columella. On the right the mold supporting the skin graft is in position in the nasopharynx.

lumen by means of two heavy silk ligatures attached to its upper surface and brought out through the nostrils. Although the sponge rubber mold was of such size and shape as to be self-retaining, supplementary anchorage was deemed advisable and was secured by tying the traction ligatures mentioned previously together below the columella over a small rubber tube. In addition the edge of the palate and the pharyngeal incision were sutured directly to the skin graft and the mold supporting it.

Treatment with penicillin was continued postoperatively and the patient's convalescence was uneventful. The mold was removed for inspection of the graft on the tenth day. Complete take of the graft had been obtained. At the end of two weeks the sponge rubber mold was replaced with a self-retaining acrylic obturator and the patient was dismissed from the hospital. The obturator was taken out for cleansing on alternate days and was worn for approximately two weeks.

The patient was dismissed from the clinic on the thirty-third postoperative day. At that time the nasopharyngeal lumen measured approximately 1.5 cm. and had shown no tendency to contract since removal of the obturator a week previously.

INFECTION OF THE NECK AFTER TONSILLECTOMY*

CLIFFORD F. LAKE

Fortunately infection of the neck after tonsillectomy is not a common occurrence when considered in relation to the large number of tonsillectomies performed. However, when such infection does occur it is dangerous and demands prompt, rational treatment.

Infections of the neck may be represented by cervical adenitis, cellulitis of the neck, infection of a fascial space, thrombophlebitis and septicemia or any combination of these conditions.

ETIOLOGY AND PROPHYLAXIS

Obviously infection of the neck after tonsillectomy results from invasion of one of the cervical structures by pathogenic bacteria. The avenue of entrance of such bacteria into the neck cannot be determined definitely. Certain conditions already present in the patient's throat and trauma incident to surgery may predispose to postoperative infection. The presence of an active infection of the throat or a common cold may predispose to infection of the neck after tonsillectomy. Injury to the superior constrictor muscle, which lies between the tonsil and the pharyngomaxillary space, conceivably may predispose to infection of this space. Undue trauma incident to performance of tonsillectomy, especially that caused by dissection of the lower pole of the tonsil from its rather firm attachment to the superior constrictor muscle, may produce an avenue of infection to the pharyngomaxillary space.

In introducing a local anesthetic agent great care should be employed to direct the needle properly, especially in the region of the lower pole of the tonsil, wherein deep insertion of the needle might readily cause penetration of the superior constrictor muscle. At the lower pole the needle should be directed into the plica in a direction horizontal to the palatoglossal muscle in order to avoid penetration of the superior constrictor muscle. All injections about the tonsil should be made into the plane which lies between the tonsillar capsule and the aponeurosis of the superior constrictor muscle; the needle should be felt to move freely in this plane. The use of unsterile equipment in administration of injections obviously may lead to infection of the neck.

Occasionally the styloid process produces a convexity or "tenting effect" in the otherwise concave tonsillar fossa; if this condition is not recognized, undue trauma to the tonsillar fossa may result from operation. Obviously, if careful dissection is done, injury to the tonsillar fossa should not occur.

From a bacteriologic standpoint, the virulence of the invading organism is undoubtedly of great importance.

Such diseases as diabetes, chronic nephritis or other severe constitutional diseases, although they may not actually predispose to infection of the neck, certainly make the patient less resistant once infection has developed.

* Abridgment of paper published in full in *Minnesota Medicine* 30:851-853, 1906 (Aug) 1947.

ANATOMIC CONSIDERATIONS

From a pathologic standpoint knowledge of the anatomy of the neck, especially that of the fascial planes, is important. It is especially important that every practitioner of otolaryngology be familiar with the pharyngomaxillary space, which lies very near the tonsil. It should be understood that the pharyngomaxillary space in the normal neck is merely a potential space and that only as a result of the formation of an abscess within it or of the introduction of the dissector's finger or instrument into it does this potential space become an actual space or compartment.

The pharyngomaxillary space is pyramidal in shape; its base is the skull and its apex is at the greater cornu of the hyoid bone. The lateral boundary consists of the parotid space and fascia. The internal pterygoid muscle and the ascending ramus of the mandible form the anterior boundary. The superior constrictor muscle separates the pharyngomaxillary space from the tonsil and provides the medial boundary of this space. Posteriorly the space is bounded by the stylopharyngeal aponeurosis which covers the great vessels of the neck.

SIGNS AND SYMPTOMS

Deep infections of the neck frequently have an insidious onset, although those which follow tonsillectomy may have a rapid onset. The temperature rises daily to peaks, then may level off and gradually fall. Chills and sweats commonly occur. Various degrees of toxemia may exist. Dysphagia and dyspnea may be present. The patient complains of pain in the throat and neck. At examination, some evidence of tenderness can be elicited. In infections of the pharyngomaxillary space trismus, swelling in the region of the parotid gland and displacement of the tonsillar fossa and the palate occur. The patient who has infection of the pharyngomaxillary space should be observed closely for symptoms and signs of phlebitis.

TREATMENT

There are two schools of thought in respect to treatment of deep infections of the neck: those of one school favor early opening of the lesion, while those of the other favor the relatively conservative practice of waiting for appearance of signs of fluctuation or of localization of the infection before institution of drainage. Use of hot packs and irradiation may prove beneficial. The sulfonamide drugs and penicillin are valuable in combating infections caused by organisms which are sensitive to the action of these therapeutic agents. General supportive measures should be instituted. If dysphagia is severe a feeding tube should be inserted. Should involvement of certain structures cause dyspnea, tracheotomy should be performed. The value of blood transfusions should not be forgotten.

Incision for opening an infected pharyngomaxillary space is made from below and behind the angle of the mandible forward on a line toward the hyoid bone. The T incision of Mosher may also be used. After the superficial structures have been separated, the finger is inserted in the space between the parotid and submaxillary salivary glands medial to the mandible and pushed along the inner aspect of the internal pterygoid muscle into the pharyngomaxillary space. A large rubber-dam type of

drain should be inserted deeply into the space and a suitable dressing applied.

If thrombophlebitis of the internal jugular vein has taken place the incision should be extended down over the course of the vein so that adequate exposure of the vessel may be secured to permit treatment of this complication.

SUMMARY AND CONCLUSIONS

Infection in the neck following tonsillectomy is dangerous. Tonsillectomy should not be carried out in the presence of acute infection in the pharynx or mouth. Great care should be employed in introducing the local anesthetic agent for tonsillectomy. Familiarity with the anatomy of the neck is important in carrying out both the infiltration for anesthesia and the tonsillectomy. After tonsillectomy all patients should be observed for signs and symptoms of the onset of infection in the neck. Should such infection occur, prompt and rational treatment should be instituted.

CARCINOMA OF THE LARYNX: METHODS AND RESULTS OF TREATMENT*

GORDON B. NEW, FREDERICK A. FIGI, FRED Z. HAVENS AND JOHN B. ERICH

In recent years, the frequency and seriousness of carcinoma of the larynx have become generally recognized, and physicians have developed an increasing interest in the treatment of this disease. As a matter of fact, the therapeutic measures designed to cure this condition have become sufficiently diversified to arouse genuine controversies in regard to policies of treatment. It is our opinion that no one method is superior to all others; on the contrary, the type of treatment to be instituted in any given case must be governed by the type and extent of the growth which is present. In support of this opinion, we wish to present the methods of treating carcinoma of the larynx at the Mayo Clinic and the end results of such management. This presentation is based on a study of 568 patients who were treated for malignant laryngeal neoplasms at the clinic during a ten year period 1934 to 1943, inclusive.

At the clinic, every patient with symptoms referable to the larynx is required to give a thorough history of his symptoms. Roentgenograms of the thorax, studies of the blood, urinalysis, serologic tests for syphilis and examination of the sputum, if indicated, are made and a general physical examination is performed. The larynx itself is examined by the indirect method and in many instances roentgenograms and tomographs of the larynx are obtained.

When on indirect laryngoscopy a lesion of the larynx is found to be fungating or ulcerated, to cause fixation of a vocal cord or to produce a metastatic mass in the neck, there can be little question concerning the

* Abridgment of paper published in full in *Surgery, Gynecology and Obstetrics*, 87:623-629 (Nov.) 1947.

nature of the neoplasm. However, on mere visual inspection, many malignant laryngeal tumors cannot be distinguished from certain benign growths, tubercnomas or syphilomas. For instance, early laryngeal epitheliomas of a projecting papillary character that have not infiltrated deeply enough to cause fixation of the vocal cord may be confused with benign papillomas. Papillary inflammatory growths often are more difficult to distinguish from papillary carcinomas than are papillomas. Occasionally an early infiltrative carcinoma without ulceration on a mobile cord can easily simulate one of many types of benign tumor. Distinguishing clinically between papillary leukoplakia or epithelial hyperplasia and papillary epithelioma often is impossible; however, such a distinction is unnecessary since thickened leukoplakia and epithelial hyperplasia always should be considered malignant until proved otherwise by microscopic examination.

Because mere visual inspection by indirect laryngoscopy cannot offer an unerring diagnosis, it becomes evident that biopsy of every laryngeal tumor is absolutely essential. We believe that removal of a specimen for biopsy is carried out most effectively under suspension laryngoscopy. We use the Lynch suspension apparatus through which an excellent view of the larynx can be obtained; it leaves both hands of the surgeon free to manipulate such instruments as are necessary for obtaining the specimen.

On our hospital service, a specimen of tissue from the larynx obtained under suspension laryngoscopy is examined at once by the frozen section method. This enables a competent pathologist to give the surgeon a definite histologic diagnosis usually in a few minutes. An immediate microscopic examination of frozen sections of tissue while the laryngoscope is still in place has two distinct advantages. First, if the pathologist finds that the first specimen of tissue is unsatisfactory for diagnosis, another piece of tissue can be obtained without delay. Second, if a laryngeal growth is found to be malignant but meets certain specifications that will be discussed later, it can be removed or treated without delay.

It seems to us that close co-operation between the pathologist and the laryngeal surgeon is essential in treatment of carcinoma of the larynx. Not only is histologic examination of laryngeal tumors necessary in making an accurate diagnosis, but it is equally important in determining the degree of activity of malignant lesions. At the clinic carcinomas are graded, according to their microscopic appearance, from 1 to 4, grade 1 being the least malignant and grade 4 the most malignant (Broders' classification). The grade of malignancy is one of the very important factors in selecting the form of therapy most suitable in each individual case of carcinoma of the larynx.

It is our belief that the surgeon who assumes the responsibility of obtaining a specimen for biopsy from a laryngeal tumor should be competent and prepared to treat the lesion. If a specimen of tissue is removed by someone else before the surgeon sees the patient, it often is difficult for the surgeon to determine the extent of the lesion. Such a circumstance can jeopardize the patient's chance for a cure by a conservative operation; the surgeon, not knowing the exact limits of the growth, may find it necessary to perform a more radical surgical procedure than would have otherwise been necessary.

We would like to reaffirm our opinion that accurate diagnosis is essential in the care of malignant laryngeal neoplasms. Accurate diagnosis is based

on thorough physical examination, indirect and suspension laryngoscopic examinations and detailed histologic examination of a specimen of the tumor.

TREATMENT

At the clinic, four methods are used for treatment of carcinoma of the larynx. They may be listed as follows: (1) thyrotomy (laryngofissure) and surgical removal of the growth, (2) laryngectomy, (3) removal or treatment of the local lesion under suspension laryngoscopy and (4) external irradiation. The selection of the most suitable method in each individual case of carcinoma of the larynx is based on four factors: (1) size, location and extent of the laryngeal growth, (2) grade of malignancy, (3) presence or absence of extralaryngeal extensions of the disease or metastasis to the cervical nodes and (4) age and general physical condition of the patient.

All of these factors must be considered carefully in determining just what type of treatment should be employed in each case. Complete removal of the neoplasm is the prime consideration in any of the operative procedures, but unnecessary sacrifice of the voice should be guarded against. A radical operation should not be employed when a conservative one will remove the neoplasm equally well and will leave the patient with a good functional voice. On the other hand, a conservative operation should not be used when a more radical procedure is indicated, as when the neoplasm is highly malignant and has probably extended beyond its apparent limits.

It always is a poor plan to try some conservative form of treatment with the assumption that, if the results are not good, something else can be attempted later on. This is detrimental to the patient's opportunity for a permanent cure as postirradiated cancer of the larynx is difficult to cure even by laryngectomy. It is well to remember that the patient who has a carcinoma of the larynx has but one good chance to get well, and if the first method fails, it is likely that subsequent methods also will fail. Consequently, the laryngologist should not use one form of treatment and then another in the hope that one of them will destroy the tumor completely. On the contrary, he should carefully consider in each individual case all of the four factors previously mentioned and decide which method is most likely to effect a cure.

It is more or less generally accepted that low-grade malignant tumors are radioresistant and, in consequence, are better treated surgically whenever possible. We believe that grade 1 or 2 carcinomas of the larynx which have not metastasized are treated more successfully by operation than by irradiation. Furthermore, in our experience, most grade 3 laryngeal cancers, if not too extensive, are also more likely to be cured by surgical means. Since about 93 per cent of laryngeal carcinomas are grade 1, 2 or 3 (table 1), it is evident that at the clinic the great majority are treated by surgical measures. It is our opinion that irradiation is the treatment of choice for grade 4 carcinomas of the larynx unless the lesion is small and well localized.

One argument sometimes advanced to discredit the surgical management of malignant lesions of the larynx is the immediate risk (hospital mortality) of such operations. However, as is shown in table 2, in 446 cases in which operation was performed at the Mayn Clinic from 1931 to 1943, inclusive, there were only 8 (1.8 per cent) hospital deaths. Furthermore, during the past seven years, due to some refinements in surgical technic and due to the

advent of sulfa drugs and penicillin, 428 patients were operated on for carcinoma of the larynx with only 2 (0.47 per cent) hospital deaths; and both of these deaths were due to coronary thrombosis. Consequently, we believe that the hospital mortality associated with surgical management of carcinoma of the larynx need be of no concern.

TABLE 1

CARCINOMA OF THE LARYNX: 416 PATIENTS OPERATED ON;
GRADE OF MALIGNANCY (BRODERS' METHOD)

Grade	Patients	
	Number	Per cent
1	64	14.4
2	212	47.3
3	139	31.2
4	26	5.8
Not stated	5	1.1
Total	416	100

TABLE 2

CARCINOMA OF THE LARYNX 416 PATIENTS OPERATED ON, HOSPITAL DEATHS*

Operation	Patients	Hospital deaths	
		Number	Per cent
Laryngectomy	213	4	1.9
Thyrotomy	184	4	2.2
Suspension laryngoscopy	49	0	—
Total	446	8	1.8

* During the last seven years 428 patients were operated on; only 2 (0.47 per cent) of these patients died.

These hospital mortality rates are low as the direct result of several factors in addition to the two mentioned. Close co-operation between trained surgeons, assistants and nurses at the time of operation and co-operation between the surgeon and physician anesthetists are contributing factors. We believe that the use of cervical block anesthesia rather than general anesthesia contributes to the lowness of our hospital mortality

rate in major laryngeal operations (thyrotomies and laryngectomies). It is obvious, of course, that satisfactory block anesthesia can be effected only by a highly skilled anesthetist. Care given by specially trained assistants and nurses during the postoperative period of hospitalization also is a favorable influence.

THYROTOMY (LARYNGOFISSURE)

No definite rules have been set down for determining which malignant tumors in the larynx can be removed by thyrotomy and which should be treated by laryngectomy. Such a decision requires experience and surgical judgment. However, the type of tumor which is ideal for removal by thyrotomy is of a low grade of malignancy and is confined to the anterior two thirds of a vocal cord which is freely movable. Carcinomas of similar type and location which have infiltrated the tissues of the cord a trifle so as to cause slight fixation of the anterior part of the cord usually still can be removed by thyrotomy providing that the portion of thyroid cartilage adjacent to the growth is removed along with the tumor. Extension of a low-grade carcinoma across the commissure does not preclude the possibility of extirpation by thyrotomy. As a matter of fact, superficial low-grade epitheliomas involving the anterior half of both cords can be removed satisfactorily by thyrotomy; the result of such an operative procedure is a rounded opening in the posterior portion of the larynx which offers the patient an adequate airway and a fair voice. Small, well-circumscribed, high-grade epitheliomas confined to a portion of the anterior two thirds of a freely movable vocal cord often are curable by wide excision and electrocoagulation through thyrotomy exposure.

Thyrotomy frequently is performed for exploration of the larynx to render the neoplasm visible; it often is impossible to determine preoperatively whether the growth should be removed in a conservative manner or whether laryngectomy should be done. Some well-circumscribed supraglottic cancers, too extensive to be extirpated through a laryngoscope, can be removed by thyrotomy, although many require laryngectomy.

Briefly, the technic of thyrotomy employed at the clinic is as follows: We use cervical block anesthesia. We believe that it is preferable for the patient to be conscious during the operation because general anesthesia is difficult to control when the laryngeal lumen is exposed through an external incision and because any blood that happens to trickle down the trachea is coughed up readily. After cervical block, the thyroid and cricoid cartilages are exposed through a median line skin incision. With a motor-driven circular saw, the thyroid cartilage then can be divided in the midline and the cut edges retracted with hooks. Incision of the underlying laryngeal mucosa exposes the interior of the larynx and the neoplasm to direct view. The lesion is excised completely with a scalpel and scissors, and the underlying bed of tissue is electrocoagulated thoroughly. The tissue which was removed is sent immediately for histologic examination by the frozen section method. If a portion of the thyroid cartilage is contiguous to the base of the electrocoagulated area, it is removed with rongeurs.

This completes the removal of the growth. A tracheal cannula is inserted just below the cricoid cartilage to insure that the airway remains adequate during the postoperative healing period, a matter of ten to fourteen days.

The wound is closed rather loosely with interrupted silk sutures and a split-rubber tube drain is inserted subcutaneously.

LARYNGECTOMY

At the clinic, all patients who have intrinsic laryngeal carcinomas which have infiltrated deeply enough to produce fixation of one or both vocal cords but which have not metastasized to the cervical nodes undergo laryngectomy providing that their age and general condition will permit. Some low-grade carcinomas which show no clinical signs of metastasis but which have perforated the thyroid cartilage or the thyroepicoid membrane or have extended into the posterocricoid region can be treated by laryngectomy with a good chance of permanent cure; in such cases, because the lesion is radioresistant, it would probably recur after irradiation. Furthermore, we have found that the possibility of curing a patient who has a low-grade malignant lesion which is undergoing metastasis to the cervical nodes is greater when block dissection of the nodes and laryngectomy are carried out than when irradiation alone is given.

As was mentioned in the discussion of thyrotomy, small high-grade epitheliomas on the anterior two thirds of a vocal cord often can be removed satisfactorily by thyrotomy. However, unless they are extremely small, all high-grade carcinomas involving a vocal cord should be treated by laryngectomy even though there be no fixation of the vocal cord. This assertion is based on the fact that very active epitheliomas often extend far beyond the apparent limits of the growth. If a high-grade malignant laryngeal lesion shows any evidence of cervical extension or metastasis, much more will be accomplished by irradiation than by surgical measures.

In performing laryngectomy, we always employ local anesthesia by means of a cervical block. We do not favor use of general anesthesia for the reasons previously given in the discussion on thyrotomy. For surgical removal of the larynx, we prefer a median line skin incision to expose the thyroid and cricoid cartilages and anterior surface of the body of the hyoid bone. This incision is carried down below the opening in the trachea. In order to facilitate exposure of the larynx, the body of the hyoid bone is divided at the midline by means of large bone forceps and the divided ends are drawn forcibly apart by claw retractors. The attachments of the muscles at the sides of the larynx are severed and the trachea is cut across. Usually, a tongue-shaped flap of laryngeal mucous membrane over the posterior part of the cricoid cartilage is elevated and left attached to the trachea; this flap ultimately aids in closure of the skin around the tracheal opening. The larynx, now detached from the trachea, is elevated and the pharyngeal mucous membrane is incised to expose the interior of the hypopharynx. By cutting across the thyrohyoid membrane, the larynx is freed completely.

On removal of the larynx, a triangular-shaped opening into the pharynx remains. This opening is closed by suturing its edges tightly in T-shaped fashion with two rows of interrupted catgut stitches. The skin margins of the wound are sutured with silk around the trachea and the flap of laryngeal mucous membrane previously described. Mattress silk sutures are used to approximate the skin edges just above the tracheal opening. After penicillin powder has been dusted into the wound, a double Penrose drain is inserted

at the median line above the mattress sutures, and the wound is closed completely with interrupted silk sutures. For a few days postoperatively, the patient is given intramuscular injections of penicillin.

During recent years, there has been considerable controversy in the literature as to whether or not tracheotomy should be performed preliminary to laryngectomy. We believe that if the patient is young or middle aged, is in good health and has a fairly adequate airway, there need be no hesitation in performing laryngectomy without preliminary tracheotomy. Removal of the larynx in one stage has two advantages. First, it saves the patient considerable time in hospitalization. Second, it is easier in many respects to remove the larynx when the patient has not undergone preparatory tracheotomy. If the airway of a patient who has a laryngeal carcinoma is badly obstructed, if his general health is poor or if he is elderly, we believe that a tracheal cannula always should be inserted in advance of laryngectomy. When a cannula is inserted, removal of the larynx is postponed for two or three weeks after tracheotomy to permit all of the inflammatory reaction attending the tracheotomy to subside. It is important that there be no inflammation when laryngectomy is carried out.

SUSPENSION LARYNGOSCOPY

Destruction of certain laryngeal carcinomas with surgical diathermy under suspension laryngoscopy is advisable in selected cases. The choice of patients for this form of conservative treatment, however, should be made only by a laryngologist with extensive experience. Small low-grade epitheliomas on vocal cords which are not fixed can be removed by surgical diathermy under suspension laryngoscopy with good results. Some laryngologists will perform thyrotomy to extirpate a very small inactive carcinoma that could have been removed by surgical diathermy under suspension laryngoscopy with much less risk and with just as good a prognosis. We wish to emphasize the fact that it is only small lesions on the vocal cords which can be treated occasionally in this conservative manner; if the neoplasm cannot be brought under direct view in its entirety or if there is any question as to the extent of the growth, thyrotomy should be performed.

In cases of low-grade cancer of limited extent on the anterior two thirds of the vocal cords of elderly patients who have hypertension, diabetes or bronchiectasis or in cases in which the patient's general physical condition is so poor as to contraindicate more radical measures, treatment under suspension laryngoscopy gives the patient a greater chance of a cure than could be expected if irradiation were used.

Well-circumscribed and low-grade malignant tumors of the epiglottis, aryepiglottic folds or base of the tongue can be treated with gratifying results by electrocoagulation under suspension laryngoscopy. After such a neoplasm has been removed by means of surgical diathermy, radon seeds often are inserted into the base of the lesion. Preliminary tracheotomy is carried out in all of these cases.

Highly malignant neoplasms of limited extent involving the epiglottis, base of tongue and occasionally the postcricoid region often can be treated under suspension laryngoscopy by implantation of radon seeds and supplementary external roentgen therapy is given; it is surprising how frequently

satisfactory results are obtained in such cases with this combined form of therapy.

In treatment of laryngeal carcinoma under suspension laryngoscopy, the pharynx and larynx first are cocaineized thoroughly. Then pentothal sodium is given intravenously and oxygen is administered through an intranasal tube that extends into the pharynx. Adjustment of the suspension apparatus offers an excellent direct view of the interior of the larynx. The surgeon has both hands free to insert and manipulate those instruments which are necessary to obtain a specimen for biopsy, to destroy a lesion by surgical diathermy or to implant radon seeds.

IRRADIATION

At the clinic irradiation of laryngeal carcinomas is a form of therapy reserved for high-grade, radiosensitive lesions which are too extensive to warrant treatment by surgical measures. Administration of roentgen rays in fractional doses is extremely important in the treatment of some carcinomas of the larynx; many high-grade tumors in which surgical operations would be of no value can be cured by fractional roentgen therapy. However, we have found that only a small percentage of laryngeal cancers are highly active growths and, in consequence, we employ irradiation as a primary form of treatment rather infrequently.

The only low-grade neoplasms which we treat by irradiation are those which are too extensive to be removed surgically and those which occur when the patient's age or general physical condition will not permit of surgical therapy.

In the majority of cases of carcinoma of the larynx in which intensive roentgen therapy is to be used, preliminary tracheotomy is to be recommended whether or not the patient's airway is badly obstructed by the growth. If tracheotomy is performed, there need be no concern in regard to the patient's airway should this become obstructed by postradiation edema.

END RESULTS OF TREATMENT

As previously stated, 568 patients were treated for carcinoma of the larynx at the Mayo Clinic from 1934 to 1943, inclusive. Of these, 446 or 78.5 per cent were treated by surgical measures; that is, by laryngectomy, thyrotomy or under suspension laryngoscopy; 122 or 21.5 per cent were treated by irradiation.

Of the 446 patients who underwent operation, 213 or 47.8 per cent were treated by laryngectomy; 134 or 41.2 per cent by thyrotomy, and 49 or 11.0 per cent by suspension laryngoscopy in which surgical diathermy was employed to destroy the growth or in which radon seeds were inserted into the growth. Of the 446 patients who underwent operation, 90.4 per cent were males and 9.6 per cent females; 80.9 per cent were between the ages of forty-five and sixty-nine years, 12.6 per cent were less than four years of age and 6.5 per cent were more than sixty-nine years of age.

Of all patients who underwent operation and who could be traced, 73.5 per cent survived five years or more without recurrence of the growth (table 3).

Of the traced patients who were treated by laryngectomy, 60.2 per cent

lived five or more years after operation; 46 per cent of the lesions were graded 1 or 2 and 54 per cent were graded 3 or 4.

TABLE 3
CARCINOMA OF THE LARYNX: FIVE YEAR SURVIVAL RATES ACCORDING
TO TYPE OF OPERATION

Operation	Patients*		Lived five or more years after operation	
	Total	Traced	Number	Patients traced, per cent
Laryngectomy	104	89	53	60.2
Thyrotomy with excision or diathermy	95	73	61	83.6
Suspension laryngoscopy with excision or diathermy	23	21	22	91.7
Total	227	183	136	73.5

* Inquiry as of January 1, 1943. Included here are only those patients operated on five or more years prior to the date of inquiry; that is, 1939 or earlier.

Of the traced patients who underwent thyrotomy, 83.6 per cent lived five or more years after operation; 61 per cent of these neoplasms were graded 1 or 2 and 39 per cent were graded 3 or 4.

TABLE 4
CARCINOMA OF THE LARYNX: FIVE YEAR SURVIVAL RATE OF PATIENTS
TREATED BY IRRADIATION

Treatment	Patients*		Lived five or more years after treatment	
	Total	Traced	Number	Patients traced, per cent
Tracheotomy and irradiation	35	32	3	9.4
Irradiation	41	40	2	5.0
Total	76	72	5	6.9

* Inquiry as of January 1, 1945. Included here are only those patients treated five or more years prior to the date of inquiry; that is, 1939 or earlier.

Of the traced patients treated by surgical diathermy or insertion of radon seeds under suspension laryngoscopy, 91.7 per cent lived five or more years

after operation; of the lesions in these cases, 82 per cent were graded 1 or 2 and 18 per cent were graded 3.

Of the traced patients who were treated by irradiation, 6.9 per cent lived five or more years after operation (table 4); of these, 46 per cent underwent preliminary tracheotomy.

The lower survival rate associated with laryngectomy is to be expected because all malignant lesions treated by this method were large, some had extralaryngeal extensions at the time of operation, and some eventually gave rise to metastasis. The high survival rate of patients treated under suspension laryngoscopy can be attributed to the fact that these patients were selected carefully and the lesions were of low grade. The low survival rate of patients treated by irradiation is to be expected since practically all of the patients had inoperable lesions, the majority of which were considered completely hopeless when first examined at the clinic. This low survival rate should not be considered as an indication of the therapeutic value of irradiation in the treatment of carcinoma of the larynx; physicians who elect the use of irradiation in cases which we would consider surgical doubtless can produce statistics which show a much higher survival rate than table 4 reveals.

COMMENT

We would like to express our conviction that carcinoma of the larynx is a curable disease, particularly when diagnosed accurately and early. However, we believe that no one form of therapy is superior to all others in the treatment of this disease. On the contrary, the type of growth in question, its activity, extent and location and the age and general physical condition of the patient should be the factors which determine what type of treatment should be instituted in each individual case. In general, low-grade laryngeal carcinomas should be treated by surgical measures while extensive high-grade, radiosensitive tumors require irradiation. Successful surgical therapy for carcinoma of the larynx is not a question of operative technic alone but of the co-ordinated and collective efforts of the surgeon, pathologist, anesthetist, assistants and nurses.

DIFFERENTIATION, CAUSE AND TREATMENT OF CERTAIN COMMON TYPES OF HEADACHE*

HENRY L. WILLIAMS

CONCLUSIONS

Inflammation or pressure within the sinuses only rarely causes headache and so-called sinus headache can nearly always be ascribed to some other cause, sinusitis being as a rule a painless disorder.

Brief outline forms of the clinical patterns of some of the conditions discussed in this paper, which may be of help in the differential diagnosis of these conditions, are listed here.

* Abstract of paper published in full in the American Academy of Ophthalmology and Otolaryngology: 1947 Graduate Lecture, Course No. 332, 17 pp.

1. **Myositis.**—Myositis is a relatively painless condition occurring in a very ill patient. It is mentioned merely to call attention to the frequent error of terming muscular headache "myositic."

2. **Muscle Strain.**—Tearing of muscle fibers by a sudden unexpected exertion may produce referred pain in the head if the tear occurs in the nuchal muscles. An area of tenderness may be elicited; the incident that produced the trauma is recalled; the pain is relieved by rest, heat and light massage and is made worse by mild exercise.

3. **Clinical Pattern of Fatigue Headache.**—Fatigue headache is a painful condition in the head due to muscle tension secondary to fatigue.

a. The headache tends to be bilateral; it occurs in the nuchal region and is referred forward to the frontal region.

b. Tenderness in the neck or head is usually not present.

c. The pain is of the aching quality characteristic of pain originating from muscle and it tends to be referred.

d. The headache tends to affect persons, such as typists and truck drivers, who hold their heads in constrained positions for long periods.

e. The headache is relieved by rest; it tends to be "dirotic," as it occurs in the late morning, is relieved by the noon rest and again appears in the afternoon.

f. The headache is not influenced by changes in temperature or atmospheric pressure; "jelling" is not present but some relief may be obtained by mild exercise, especially exercise which transfers the stress of maintaining the position of the head to other groups of muscles.

g. Salicylates will produce relief.

h. Heat and massage applied to the nuchal muscles will relieve the pain but correction of posture and caution against maintaining the head too constantly in one position are of greatest importance.

4. **Clinical Pattern of Anxiety-tension Headaches.**—This type of headache is due to tension in the nuchal muscles and is secondary to emotional stress.

a. The headache is bilateral in the occipital and frontal regions

b. Tenderness is not a feature of this type of headache.

c. The headache varies with the emotional state of the patient. Since the patients often are unable to obtain relaxation during sleep, the headache may be worse on waking and better after work which has occupied the patient's attention sufficiently to release some of the tension caused by introspection.

d. Practice of progressive relaxation, as recommended by Jacobson, or removal of emotional blocks by study of semantics, as recommended by Wendell Johnson, may prove effective.

5. **Clinical Pattern of Myalgia.**—Myalgia is characterized by tender areas in muscle with acute exacerbations of referred pain, apparently on the basis of a physical or intrinsic allergy.

a. Tender areas are present in certain definite muscles and tend to be unilateral. In the head and neck the muscles that tend to be involved are (1) the upper border of the trapezius; (2) the splenius capitis; (3) the sternocleidomastoid; (4) the stylohyoid muscle and the anterior belly of the digastric muscle; (5) the muscles attached to the alae of the thyroid cartilage; (6) the posterior crico-arytenoid; (7) the mylohyoid; (8) the insertion

of the glossopalatinus into the tongue, and (9) the superior constrictor of the pharynx. The last muscle may be involved alone, giving rise to the occasionally puzzling syndrome of myalgia of the pharynx.

b. Myalgia is not infrequently associated with other conditions thought to be due to physical or intrinsic allergy. These are the vasodilating pain syndrome, vasomotor rhinitis and endolymphatic hydrops.

c. After appropriate stimulation, the tenderness of the areas in muscle may undergo severe exacerbations which are associated with reference of pain to a distance in a distribution seemingly not that of the sensory roots but rather myotomic.

d. The referred pain is of a deep, aching character; it resembles pain from muscle and deep structures and tends to be felt at a distance from the actual source.

e. Infiltration of the tender portion of the muscle with procaine will temporarily, and sometimes permanently, abolish the tenderness and the referred pain. Infiltration of the region of reference has no effect on the referred pain.

f. Severe exacerbations of pain may be produced by environmental changes such as approaching storms, damp, rainy weather, drafts, air conditioning and the like.

g. "Jelling" is not present and no relief is afforded by mild exercise. Even the slightest use of the involved muscle tends to make the condition worse.

h. Relief may be obtained by heat and massage. Such treatment tends to accentuate the symptoms at first but, if continued, it will produce more or less permanent relief.

i. The first appearance of this clinical pattern may have been associated with an acute febrile illness, with the menopause or with severe exposure to the elements.

j. Vasodilators, such as niacin, histamine, magnesium sulfate and neostigmine, will produce prompt and lasting relief in a high percentage of cases.

k. The salicylates produce slight to very moderate relief of the pain and tenderness.

l. No permanent or transient pathologic change can be demonstrated by biopsy.

m. The disorder almost never appears before the third decade of life.

6. Clinical Pattern of Primary Fibrositis.—Primary fibrositis is a circumscribed painful condition of unknown cause in the fibrous tissues.

a. It is not related to disease of joints.

b. The pain does not tend to recur in the same sites but appears here and there at intervals.

c. The pain is characteristic of that from fibrous tissues—a burning quality. It does not tend to be referred.

d. Atmospheric changes tend to produce exacerbations.

e. "Jelling" or increased stiffness with disuse is present and relief can be secured by mild exercise.

f. "Dicrotic" symptoms may be present if too much physical effort is indulged in.

g. Temporary relief may be obtained by the use of heat and massage.

h. Vasodilators produce only as much relief as could be expected from the increased warmth brought to the area by the vasodilatation produced (slight relief).

i. The salicylates produce prompt and marked relief.

j. Slight leukocytic infiltration has been noted on pathologic examination.

k. Symptoms tend to appear first in the third and fourth decades.

7. Clinical Pattern of Secondary Fibrositis.—Secondary fibrositis is a painful condition in the fibrous tissues adjacent to a joint involved in an arthritic change.

a. Articular changes can be demonstrated by roentgenography.

b. The painful areas are in association with the involved joint.

c. Tenderness is localized about the involved joint.

d. The pain is of a severe, burning quality and does not tend to be referred to a distance unless a sensory nerve is involved.

e. The pain tends to be exacerbated by atmospheric changes and changes in temperature.

f. "Jelling" (stiffening with disuse) is present and the symptoms are relieved by mild exercise.

g. The symptoms may be "dicrotic" if too much physical effort is indulged in.

h. Primary relief may be obtained by application of heat and massage to the involved area.

i. Vasodilators produce only as much relief as could be expected from the increased heat brought to the area by the use of vasodilatation (slight relief).

j. Salicylates produce prompt and marked relief.

k. Moderate leukocytic infiltration can be demonstrated in excised portions of the tender regions.

l. Symptoms tend to appear in the third and fourth decades of life.

8. Clinical Pattern of the Temporomandibular Syndrome.—The temporomandibular syndrome is a temporal or bitemporal headache originating from the muscles of mastication and from the fibers of the temporomandibular joints.

a. Closure of the "bite" resulting in a dislocation of the stresses on the muscles of mastication may produce pain that is referred to the temporal region.

b. Tearing of the anterior portion of the joint capsule resulting from extraction of molars with the patient under general anesthesia may result in pain in the region of the joint.

c. Closure of the "bite" will produce a daytime headache while injury to the joint capsule is likely to produce pain at night when the mandible drops during sleep.

d. Closed "bite" rarely produces pain. Capsular injury is a relatively more common, but still an unusual, cause of pain in the head.

9. Clinical Pattern of Histamine Cephalalgia.—*a.* The condition is characterized by deep pain sudden in onset and termination. Pain is usually unilateral but may be midline or bilateral.

b. The painful seizure is associated with vasomotor rhinitis on the homolateral side and with other signs of parasympathetic overaction.

c. The pain may be temporarily controlled by pressure over the arteries on the involved side. The vessels are tender to palpation. On release of pressure the pain will come flooding back.

d. The pain is likely to occur during sleep and is less severe in the erect than in the recumbent position.

e. The pain may be precipitated by the ingestion of alcohol.

f. Injection of histamine, in insufficient dosage to produce a histaminic headache, will precipitate the pain after a latent period.

g. A history of precipitation of the pain by refrigeration may be obtained.

h. A history of the appearance of the syndrome following acute infection may be obtained.

i. Vasoconstrictors will relieve the pain.

j. Vasodilating pain of any severity may be associated with myalgia and *Mènière's disease* as well as with *vasomotor rhinitis*.

k. Histamine cephalalgia rarely appears before the third decade of life.

l. There is no histologic evidence of an inflammatory basis for vasodilating pain of any type.

m. Treatment with nincin or histamine may relieve all types of vasodilating pain in a high percentage of cases.

10. **Clinical Pattern of Migraine.**—In cases of migraine, an inherited familial defect allows the development of vascular spasm which is followed by overdilatation of the extracranial and intracranial arteries; in other words, there is a failure to compensate for fluctuations of arterial blood volume.

a. A family history of attacks of migraine usually can be obtained.

b. The onset of symptoms often occurs before the second decade.

c. A history of visual symptoms (including photophobia) can be obtained in about a third of all cases.

d. The headache of the deep type is pulsating. It usually is lessened by lying down and it frequently can be controlled by pressure over the extracranial vessels or by vasoconstricting drugs such as ergotamine tartrate or dihydro-ergotamine tartrate. Epinephrine, however, merely transfers the site of the headache.

e. An attack frequently is precipitated by excitement, nervous fatigue, relaxation, hunger or menstruation.

f. An increase of the flow of urine frequently occurs before or during an attack.

SOME TECHNICAL PROCEDURES IN THE TREATMENT OF CLEFT LIP AND PALATE WITH ESPECIAL REFERENCE TO THE CLOSURE OF COMPLETE ANTERIOR PALATAL CLEFTS*

FRED Z. HAVENS

In considering the surgical treatment of harelip, Blair once said: "If he learns to use any one of the standard methods the surgeon who essays the correction of nose and lip defects will expend his energy to greater profit than if he attempts to exercise eclecticism or more dangerous yet to contrive new methods. It is true that operative skill rather than breadth of acquaintance will bring greater satisfaction to the patient thus afflicted. This statement is made with no intention of belittling invention or ingenuity but rather to urge that these qualifications be directed, in the case in hand, toward adapting some well tried out plan."

Several interesting comments were made by the discussers of a recent paper by Vaughan. One said, "There is no single procedure which will correct every lip (and . . . nostril) satisfactorily." Another said, "Each makes his own modifications even if he doesn't realize it." Still another said, "The method . . . should be adapted to the individual situation."

To these comments I should like to add that the best results in the correction of harelip and its associated nasal deformities will be obtained by the surgeon who is best able to analyze the problems of the case in hand, and to choose the best well-tried plan, and finally who has the operative skill to carry out his plan.

Procedures for the repair of harelip have been thoroughly described and discussed by numerous authors. For the single harelip the Mirault operation popularized by Blair and later so well redescribed and modified by Brown is a most excellent procedure and is applicable in a large percentage of cases. It may be necessary, however, to make modifications in order to cope with special problems. The Rose operation occasionally is preferable, especially in cases of incomplete harelip.

In considering the management of the accompanying nasal deformity, emphasis is to be laid, as has been done previously by various authors, on the necessity of building a good floor for the nostril, of freeing the tissues widely so that the nose comes into proper relationship to the face as a whole and, finally, of making the necessary dissections in order to mobilize the alar cartilages so that they can be brought into as nearly normal position as possible. Blair, Brown and McDowell, Vaughan, Davis and others have described these methods well.

For bilateral complete harelip, the Thompson operation combined with closure of the alveolar and anterior palatal clefts by the Veau procedure has given excellent results. This will be considered later.

Surgical procedures for the repair of clefts of the palate also have been thoroughly discussed and described. For the repair of these clefts which involve only the soft palate or the soft palate and the posterior half to two thirds of the hard palate, I have employed the Wardill type of operation

* Read at the meeting of the American Medical Association, Atlantic City, New Jersey, June 8 to 13, 1947.

cannot be relied on to compensate for insufficient relaxing dissection. My experience has been that palates closed as described heal with less reaction than when closed with heavy catgut or nonabsorbable suture material. Only rarely is there a postoperative perforation.

After the closure has been completed, a moderately firm iodoform gauze pack is placed in the lateral wound on each side. Especial attention should be given to placing the pack well down into the space created in the region of the divided hamular process. The packs are left undisturbed for fourteen days.

Repair of the incomplete clefts of the palate usually is deferred until the patient is fourteen to sixteen months of age.

For complete clefts of the palate, either single or bilateral, I prefer the Veau type of operation for the repair of the cleft of the anterior palate and of the alveolar process. This method has been described by Ivy and Curtis but its value warrants re-emphasis.

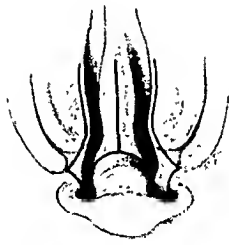


Fig. 73—Incisions for Veau type of repair of cleft of alveolar process and anterior palate.

In the Veau operation a flap is created on each side of the cleft; on the medial side it is obtained from the septal mucosa, and on the lateral side, from the lateral nasal mucosa.

An incision is made lengthwise along the middle of the exposed inferior border of the septum. This incision begins at a point opposite the second bicuspid or first molar tooth and is carried forward to a point on the premaxilla near the future margin of the gum. The incision then is continued around the premaxilla on the side toward the cleft and follows a line just inside the future margin of the gum (fig. 73). After it has been continued around the premaxilla, it passes upward a short distance to a point on the lower anterior lateral surface of the septum where it will be joined by an incision which will be made later to remove the vermillion line from the prolabium and which will be carried up into the future floor of the nostril

just lateral to the base of the columella. A periosteal elevator is used to loosen the mucosa from the septum and from the lateral aspect of the premaxilla throughout the length of the incision. It is difficult to elevate the mucous membrane from the oral and lateral aspects of the premaxilla and extreme care is necessary to avoid shredding the mucous membrane.

Next, an incision is made along the lateral margin of the cleft, beginning opposite the starting point of the septal incision. This is carried forward onto the alveolar process just lateral to the cleft and to a point near the future margin of the gum. It is then continued around the medial end of the cleft alveolar process on a line just inside the future margin of the gum and finally up inside the ala to a point where it will join an incision which will be made later to create a flap from the mucosa of the lateral portion of the labial cleft and which will be carried up into the future floor of the nostril just inside the ala (fig. 73). A periosteal elevator is used to loosen the mucosa from the lateral side of the cleft (lateral nasal wall) and from the medial extremity of the cleft alveolar process throughout the length of the incision

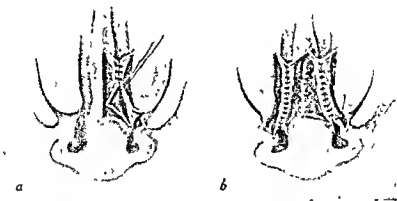


Fig 74.—Suture of flaps of mucous membrane; *a*, knots are placed on nasal side of closure; *b*, bilateral simultaneous closure.

The two flaps thus created are sutured together with no. 0000 plain catgut. Interrupted sutures are used and are placed so that the knots lie on the nasal side (fig. 74*a*). The closure must be carried across the alveolobuccal fold to make a complete floor for the anterior nasal cavity (fig. 74*b*). In the repair of the harelip which follows immediately, the floor of the nasal vestibule is made from the skin adjacent to the base of the ala and of the columella. Owing to the placement of the connecting incisions which have been described, this vestibular floor becomes an extension of the floor of the anterior nasal cavity.

In the Veau operation as originally described, a flap is made by elevating the soft tissue from the oral surface of the anterior palate and this flap is turned across to cover partially the line of closure of the flaps that have been described. The use of this flap from the palate has been discontinued. If the flaps from the septum and lateral nasal mucous membrane are prepared so that they can be sutured without tension, they will unite through-

out the entire closure and in the process of healing the raw surface on the oral side will be covered by scar epithelium. The result is that there is an intact floor for the anterior nasal cavity together with complete closure of the alveolar cleft and of approximately the anterior half of the hard palate (figs. 75 and 76). Later, a Wardill type of operation can be used to complete



Fig 75a.—Complete cleft of left lip, alveolar process and palate; b, appearance after repair of lip, alveolar process and anterior palate at one operation; c, impression made one year later. The palate is closed to a point approximately opposite first molar tooth. Wardill type operation will be used to repair remainder of palatal cleft.

the repair of the palate, or palatal flaps can be grafted and a "push-back" operation done.

In cases of single palatal cleft and associated single harelip, the Veau type of closure of the anterior palate and of the alveolar process is combined in a single stage with a Mirault type of repair of the harelip.



Fig 76a.—Complete cleft of palate and alveolar process on right side; there was only a notch in the left alveolar process; b, appearance after single-stage repair; c, impression made eighteen months after operation, compare repaired right alveolar cleft with left alveolar process which was only notched.

In cases of bilateral complete cleft palate and bilateral harelip, the bilateral Veau operation and the bilateral repair of the harelip sometimes can be done as a single operation or the anterior palate and lip on one side only can be repaired at one time and the same operation done on the other side after an interval of ten days to two weeks (fig 77a and b). Often, the decision whether to use the single-stage or the two-stage method is not made

until the defect on one side has been repaired. If the operation thus far has proceeded smoothly and if the child is taking the anesthetic well and is in good condition, one can proceed with the repair of the defect on the other side; otherwise, it is better to defer the remainder of the repair until later.

In cases of bilateral cleft of the palate and lip, the Thompson method for repair of the lip is preferred. When the premaxilla projects badly, it usually can be forced back by digital pressure so that the lip can be closed and only rarely is it necessary to section the vomer. If section of the vomer is necessary, simple division so that the anterior segment can slide back along side the posterior segment is preferable to removing a portion of it.

I am fully aware that criticism has been made of the Thompson type of operation for double harelip. However, it is not to be expected that this



Fig. 77a —Bilateral complete clefts of palate and lip, left side of anterior palate and lip repaired at first operation; same operation was performed on right side two weeks later, Wardill type operation was used to complete repair one year later; has complete closure of palate with excellent function. b Postoperative appearance; further corrective operation on lip and nose will be done later.

severe deformity can be corrected satisfactorily by a single operation in infancy. Further plastic operations almost invariably are needed, and with such subsequent operations the plan outlined has given good results. I agree with Aufrecht, who said, "There are two results . . . one is the immediate result, the closure of the harelip, and the other is the late result."

Repair of the anterior palate and lip in cases of combined complete cleft palate and harelip, either single or double, is made when the patient is six or eight weeks of age provided, of course, that he is in proper physical condition. Closure of the posterior portion of the palate is deferred until the patient is fourteen to sixteen months of age.

The Veau operation for closure of the anterior palate and alveolar process is a tedious one and technically rather difficult, but the gratifying results will repay the surgeon who masters it.

HEMANGIOMAS OF THE MOUTH*

FREDERICK A. FIGI

Hemangiomas are often encountered about the face and neck and those presenting externally may also involve the oral cavity. However, lesions of this type limited to the interior of the mouth are only infrequently seen. Those affecting the buccal cavity alone or in conjunction with other structures at times attain considerable size, produce marked deformity and dysfunction, are subject to frequent trauma and to recurring acute inflammatory processes and may give rise to serious and even fatal hemorrhage. Treatment is advisable for many of these tumors but the type of treatment and the optimal time for administering it varies in different cases. In general, radiation is the treatment of choice for strawberry birthmarks and cavernous hemangiomas in infants and small children. In adults cavernous lesions are more effectively treated with electrocoagulation and injections of boiling water or chemical sclerosing agents. Well-circumscribed hemangiomas often are best excised. Plexiform or racemose hemangiomas usually require ligation of the afferent vessels in addition to the measures employed in treatment of cavernous hemangiomas.

PERFORATION OF ROOTS OF IMPACTED LOWER THIRD MOLARS BY CONTENTS OF MANDIBULAR CANAL: REPORT OF A CASE†

LOUIE T. AUSTIN

A definite grooving or an imprint which has resulted from pressure of the contents of the mandibular canal on the root ends of extracted, impacted or unerupted third molars is frequently noted. An intimate relationship between the canal and the root ends of the tooth exists in the lower third molar region. Patients with deeply impacted lower third molars are warned of the possibility of prolonged partial anesthesia following removal of these molar teeth due to trauma of the mandibular nerve.

REPORT OF CASE

A woman thirty-six years of age was referred to the Section on Dental Surgery for a dental examination as a part of a general physical examination. The findings were essentially negative except for incompletely erupted lower third molars (fig. 78a), extraction of which was advised. The relationship between the canal and the roots of the third molars was noted and the patient was advised as to the possibility that persistent numbness might occur after operation.

The patient was sent to surgery for the removal of the lower right third molar. With the patient under local anesthesia, the distal cusps of the tooth were split off by means of the chisel and mallet. The tooth was raised in its socket by use of a Le Cluse elevator. Perforation of the root by the contents of the canal was recognized when the tooth was withdrawn. It was

* Abstract of paper published in full in the *Annals of Otology, Rhinology and Laryngology*, 66:833-866 (Dec.) 1947.

† From the *American Journal of Orthodontics and Oral Surgery*, 33:623-624 (Aug.) 1947.

necessary to split through the root to disengage the contents of the canal. The continuity of the structures in the canal was not broken and the contents of the canal were allowed to drop back into the tooth socket. One week later the lower third molar on the opposite side was removed, a similar involvement of the tooth by the contents of the mandibular canal was found, and it was necessary to split the tooth through to the perforation to free the contents of the canal.



Fig 78 —Perforation of the roots of impacted lower third molars by the contents of the mandibular canal. *a*, Preoperative view; *b*, postoperative view.

After operation the patient was seen daily. The postoperative course was quite satisfactory with the exception of persistent anesthesia of the soft tissue of the lower lip on both sides extending distally to the region of the angles of the mouth. Postoperative roentgenograms were made (fig 78*b*) and the patient was dismissed. The appearance of the extracted teeth is shown in figure 79.



Fig 79.—Same case as in figure 78. Root ends of lower third molars showing perforation.

In this case as calcification of the root ends of the lower third molars was completed the contents of the mandibular canal become surrounded by tooth substance. In such cases there is definite evidence of constriction or narrowing of the canals illustrated in the preoperative dental films of both

third molars as they pass by, or in this instance through, the roots of the third molars.

In instances of this sort, considerable disturbance of the contents of the canal is certain to occur on removal of the teeth. Since the evidence of constriction occurred on both sides and both third molars were proved to have perforation, it is felt that this narrowing or constriction of the shadow of the canal in the dental film is a definite indication of perforation, or at least impingement, of the tooth root on the mandibular canal with the likelihood that considerable damage to the contents of the canal will occur on removal of the tooth.

THE TEETH AND THEIR SUPPORTING STRUCTURES IN PATIENTS TREATED BY IRRADIATION*

EDWARD C. STAFNE AND HARRY J. BOWING

All patients with pathologic lesions about the head and neck should be adequately studied, including consideration of roentgenograms of the head and dental system made before treatment as well as of those made at the time of the follow-up examinations.

The irradiation therapy outlined for a child should be confined to the field of involvement and the adjacent structures should be shielded as much as possible. The initial dose of irradiation should be adequate and the interval between applications quite lengthy; probably this interval should be thought of in terms of many months. The decision to repeat treatment should be based on definite evidence that repetition of treatment is necessary for a good result.

The adult patient should be prepared for irradiation treatment by prophylactic dental management. This type of dental consideration should reduce or prevent dental degeneration, caries and osteoradionecrosis as a postirradiation complication.

DENTAL ROOTS IN THE MAXILLARY SINUS†

EDWARD C. STAFNE

The shadow of retained roots of teeth superimposed on that of the maxillary sinus is often seen in the roentgenogram. Nearly all of these roots are situated in their original position in the dental alveolar socket. Roots lying free in the maxillary sinus are rarely encountered; when roots do occur in this location, they are most often recognized by a deviation from their

* Abstract of paper published in full in the *American Journal of Orthodontics and Oral Surgery* 33 567-581 (Aug) 1947.

† From the *American Journal of Orthodontics and Oral Surgery*. 33 582-584 (Aug) 1947.

normal vertical position in the arch and by an absence of the lamina dura which normally surrounds them. Some dental roots, particularly those of small size, which are forced into the maxillary sinus and are not recovered, may become incorporated in mucous secretions and may soon be eliminated through the normal sinus opening into the nostril.

In the event that a root becomes lodged between the antral mucosa and the wall of the maxillary sinus it may become a source of local inflammation or maxillary sinusitis. A root was found in this location in the following case.

REPORT OF CASE

A man forty-one years of age was referred for the removal of a root in the upper left second bicuspid region. An attempt to extract the second bicuspid had been made some time previously but there had been a failure to remove the root in its entirety. A roentgenogram revealed a root in which root canal therapy had been performed and which, because of its deviation from a normal position, appeared to have been forced from its original position in the socket (fig 80, inset). There was also a history of chronic maxillary sinusitis.

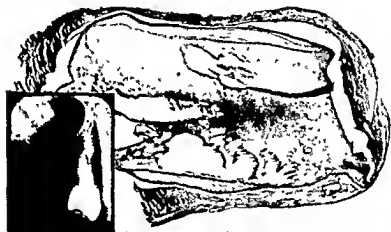


Fig 80—Longitudinal section of a root removed from the maxillary sinus; the root is surrounded by a capsule of inflammatory tissue ($\times 10$). Inset, Root in maxillary sinus.

The root was removed on January 15, 1915, with the patient under local anesthesia. An incision was made along the crest of the alveolar ridge from the third molar region to a point near the first bicuspid, from which it was extended upward and forward to the buccal fold. The flap was made sufficiently large so that when it was replaced it covered completely the opening which had to be made in the wall of the maxillary sinus. The mucoperiosteum was retracted upward exposing the lateral wall of the maxillary sinus. A slight discoloration of the bone directly overlying the root could be seen and an opening was made through the antral wall sufficiently large to deliver the root. The root was found encapsulated by a mass of soft tissue situated between the antral mucosa and the bony wall of the maxillary sinus. After removal of the root and the tissue which surrounded it the mucoperiosteum was replaced and carefully sutured.

The specimen which had been removed was decalcified and longitudinal microscopic sections were made which revealed that the root was completely surrounded by a capsule of inflammatory tissue (fig 80).

A root or root fragment which is forced into the maxillary sinus may become a nucleus for the formation of a rhinolith. Roentgenograms of a

patient who for several years had been suffering from chronic maxillary sinusitis revealed a foreign body in the left sinus. Dental roentgenograms



Fig. 81.—Dental root from the maxillary sinus encapsulated by calculus ($\times 8$). *Inset*, Root in maxillary sinus.

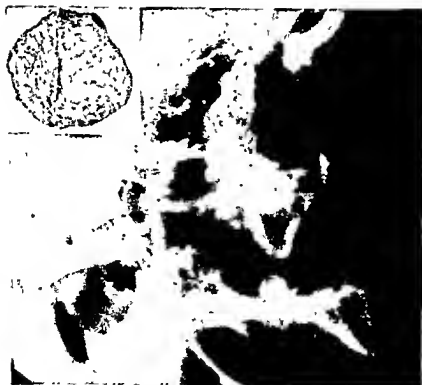


Fig. 82.—Rhinolith in the maxillary sinus. *Inset*, Rhinolith ($\times 7$)

revealed an absence of bone of the floor of the maxillary sinus in the first molar region which suggested that the object was probably a dental structure that had been forced into the sinus. The degree of radiopacity of

the periphery of the object suggested that the object might be the crown of a tooth (fig. 81, inset). After removal a longitudinal ground section was prepared which revealed that the inner portion of the object contained a dental root. The entire root was covered by a heavy deposit of calculus. A portion of the calculus became separated from the root during sectioning (fig. 81).

The degree of radiopacity of a rhinolith does not vary greatly from that of a tooth structure, and the one may be confused with the other when the image appears on the roentgenogram. A radiopaque object which appeared in the lateral view roentgenogram of a maxillary sinus proved to be a rhinolith (fig. 82). The specimen in this instance was divided in halves to determine if gross pieces of tooth structure were present in the center of the specimen, and none were seen (fig. 82, inset). Further to rule out the possible presence of dental root substance the specimen was placed in a decalcifying solution but no root substance was found. However, as a result of decalcification a thread about 1 cm. in length was found in the mass, a foreign body which probably had provided the nidus on which a deposition of calculus had been initiated.

There have been some instances in which patients have been referred for the removal of dental roots that recently had been forced into the maxillary sinus but in whom the roots were no longer present when the patients presented themselves. Therefore, it is important to make roentgenograms shortly prior to the time removal of the root is contemplated.

EXAMPLES OF DENTAL DYSPLASIA*

STANLEY A. LOVESTEDT

The dental findings may be of considerable importance in establishing a diagnosis of ectodermal dysplasia or progeria in a young person. There are clinical findings which may be more or less common to certain stages of both diseases and a knowledge of the presence or absence of teeth may be of value in establishing the differential diagnosis.

In the disease classified as "ectodermal dysplasia," there may exist many variations in the total number of teeth that are congenitally absent, the classic dental finding being anodontia with underdeveloped dental arches. In this particular study there were a few cases in which the dental findings suggested possible ectodermal dysplasia; however, the other findings were generally absent, so these cases were not indexed as ectodermal disease and, hence, not included. The marvel may be not that variations in the dentition do occur but rather that they do not occur with greater frequency.

In progeria the dentition does not seem to suffer as does the rest of the organism. There is a tendency for delayed eruption of the deciduous teeth to occur and an awareness of the overcrowding which obviously would follow the eruption of the secondary dentition because of the lack of dimensional jaw development.

* Abstract of paper published in full in the *American Journal of Orthodontics and Oral Surgery*. 33:625-629 (Aug.) 1947.

of the week. The stiffness was principally a limitation of abduction and rotation, to a variable degree. The frozen shoulder was held in the sling position and permitted no motion except some apparent forward flexion and backward extension as a result of movement of the shoulder girdle. Nineteen per cent of our patients gave a history of bilateral involvement, or the subsequent development of a similar condition of the second shoulder. Women commonly complained of inability to comb their hair or button their clothes behind them, and men were unable to get their hands into their hip pockets. The tenderness was maximal over the point of the shoulder laterally. This site corresponds to the tendinous portion of the rotator cuff near its insertion into the tuberosities of the humerus. At times there was some thickening in the overlying bursa and the calcareous plaque beneath it could be seen and palpated through the intact skin.

It goes without saying that in all cases of painful stiff shoulder a detailed history of the illness should be obtained. The next essential procedure is a complete physical examination. Examination of the heart, lungs, abdomen, pelvis, rectum and of the nervous and vascular systems should be made routinely in order that a serious disease is not mistaken for a local disorder. Finally a roentgenographic examination of the shoulder should always be made to rule out arthritis, fracture or the presence of organic bone disease, such as infection or primary or metastatic tumor, and to give evidence of the degree of osteoporosis or tendinous calcification present. In many cases osteoporosis, especially of the greater tuberosity and anatomic neck, is marked.

TREATMENT

The patient seen in the acute stage or with intense pain, local tenderness, slight fever and the arm maintained at the side for protection may be treated for a few days at home by rest in bed, local application of heat, increased intake of fluid, maintenance of elimination and traction together with doses of aspirin or codeine. Abduction should be encouraged, and later conventional diathermy and roentgen therapy can be given. Following this type of treatment patients who have painful stiff shoulders often are relieved of their symptoms. When the patient is seen in the subacute stage after much of the pain has subsided and residual soreness and stiffness, aggravated by movement, persist, examination then may be made to exclude calcification, traumatic lesion or tumor. Conventional diathermy, radiant heat, stretching and active and assistive exercises should be carried out routinely. If there is difficulty in obtaining abduction, traction may be employed, or manipulation followed by abduction treatment in a splint or cast. In cases in which definite swelling of the bursa occurs as a result of effusion or hemorrhage, aspiration should be done. If murky turbid fluid and rice bodies are present animal inoculation with the fluid or excision of the bursa and microscopic studies should be performed to rule out tuberculous.

Physical medicine, including baking, massage, diathermy and exercise, was used almost universally in the 150 cases studied irrespective of the other forms of treatment employed. In those cases in which conservative treatment, including roentgen therapy in some, had failed to give the patient relief of symptoms, surgical treatment was carried out.

For open operations on the service of one of us (H. W. M.) we usually employ an anteromedial split deltoid incision to expose the subdeltoid bursa and, as the muscle is retracted, the thickened bursa. Rotation of the arm may be required to bring into view the calcified deposit which appears as a raised whitish yellow patch surrounded by a circular band of inflamed tissue. On incision through the bursa, milky bursal fluid may be encountered. This type of fluid has been considered to result from rupture of the calcified mass. The degree of calcification in these cases varies considerably and the calcareous deposits may be granular or of "tooth-paste-like consistency." The tendon cuff may have numerous connected or distinctly separate deposits which may extend into the bone. Curettage of this calcified deposit may not remove it, as it may have permeated the degenerated fibrotic tissue to such an extent that excision may be necessary.

Since stiffness tends to persist or recur in spite of surgical excision of calcareous deposits, needling to rupture such deposits, or manipulation to break up adhesions, persistent physical therapy was employed almost routinely after operation.

At times an adjustable abduction splint or cast with traction is used. When manipulation is needed we prefer to use general anesthesia. Afterward the arm is placed in abduction and external rotation for the next forty-eight hours, by tying the patient's hand to the head of the bed. Manipulation can be extremely hazardous because of the danger of producing fracture, especially in those cases in which there is osteoporosis. If osteoporosis is extensive, the stiffness may be combated by placing the arm in abduction under traction and carrying on physical therapy. The degree of abduction is increased as improvement takes place. Local injections of procaine or blocking of the suprascapular nerve may give added benefit. Application of heat with active, passive and assistive exercises must be carried out daily and the result obtained depends to a large extent on the co-operation of the patient. Roentgenograms should be taken after operation or manipulation to exclude possible fracture or dislocation.

In sixty-nine (46 per cent) of the 150 cases of this series manipulation under anesthesia was performed; in thirty-two (21 per cent) additional cases manipulation with injections of procaine into the suprascapular nerve was used; in thirty-one (21 per cent) a needling operation was performed to pierce and break up the calcareous deposits; and in eighteen (12 per cent) surgical excision of the calcareous mass was performed.

Roentgen Therapy.—Forty of the 150 patients (27 per cent) received roentgen therapy in addition to other treatment. Some of them had it prior to admission at the clinic.

The following comments by Leddy and Popp apply to all patients with painful stiff shoulder treated by them and includes a much greater number of cases of acute lesions than of chronic. They stated that in treatment of painful stiff shoulder smaller dosage of roentgen rays are employed than those employed elsewhere, and they treat more frequently. Ordinarily the beam of roentgen rays is centered over the bursa at the point of maximal tenderness and if the condition is a very acute frozen shoulder, which cannot be moved comfortably, they give a dose of 75 r on alternate days for three to four doses. They recommend that the patient keep the arm still and use aspirin in case of pain. For the subacute type of case, they

use a dose of perhaps 100 r; for the chronic type, 100 r once or twice a week, depending on how painful the shoulder is. They have encountered a group of patients with sore shoulders who seem to become worse after roentgen therapy if physical therapy is being given at the same time. Since it cannot be determined, in advance, which patients will become worse, the patient is told to stop taking physical therapy if he becomes worse. Leddy and Popp have stated that the presence or absence of calcium in the bursa does not seem to make any difference as far as the result of roentgen treatment is concerned. About 75 per cent of the patients who have acute conditions and more than 50 per cent of those whose condition is chronic are relieved of their symptoms by roentgen treatment.

SHOULDER AND ARM PAIN*

RALPH K. GHORMLEY

Knowledge of the syndrome or syndromes of arm pain and their relation to lesions of the cervical part of the spinal column, shoulder and brachial plexus has improved slowly compared to knowledge of the sciatic syndrome.

Painful lesions of the shoulder commonly involve the capsule or musculotendinous cuff. Less frequently encountered painful lesions are those of the head of the humerus and of the scapular structures. The most common painful lesions of the shoulder are: (1) frozen shoulder, capsulitis, tendinitis, peritendinitis, or periarthritis; (2) calcified subdeltoid bursitis, subdeltoid bursitis or degeneration of supraspinatus tendon, and (3) tears of the supraspinatus tendon and of the musculotendinous cuff.

Codman must be credited with describing incomplete and complete tears of the supraspinatus tendon. He stated that among the lesions of the shoulder (exclusive of tumors, fractures and infections), calcified deposits, tendinitis, partial and complete rupture of the supraspinatus tendon have about an equal incidence.

Review of the writings of various authors reveals a varied opinion as to the incidence of lesions of the musculotendinous cuff. Although definite figures are not available on the incidence of each of these lesions, Codman's estimate may be used for the basis.

Certain facts have come to be accepted concerning painful lesions of the shoulder: 1. The supraspinatus tendon in a fair number of persons tends to degenerate and the frequency of this occurrence increases with age. 2. There is general agreement that the so-called periarthritis or frozen shoulder has its inception in some type of inflammation of the tendon or tendon sheath. 3. Calcification in bursae probably results from accumulation of degenerated tendinous material. 4. Ruptures of the supraspinatus tendon are fairly common in older persons. They may cause severe symptoms in some cases and require surgical treatment. 5. Among younger persons, following trauma, tears of the musculotendinous cuff are much

* From American Academy of Orthopaedic Surgeons annual volume. Ann Arbor, Michigan. Edwards Brothers, Inc., 1948. (In press)

more severe and serious than among older persons. Surgical repair is indicated whenever possible but in the more severe tears arthrodesis may be necessary to relieve the painful symptoms.

Lesions that have not been mentioned which may cause painful shoulder are (1) tumors and infections of the scapula or head of the humerus; (2) lesions of the clavicle; (3) lesions of the acromioclavicular joint; (4) tumors of the soft tissues about the shoulder; (5) tuberculous and other types of arthritic involvement of the shoulder, and (6) fractures or fracture dislocations of the shoulder.

The differential diagnosis of lesions of the shoulder from lesions of the cervical portion of the spinal column or brachial plexus often is a difficult problem. It must be remembered in cases of pain in the shoulder or arm that lesions of both the cervical part of the spinal column and shoulder joint may be present. The most important point in differential diagnosis is the presence of local signs in the shoulder; that is, both active and passive limitation of motion; either diffuse or localized tenderness; atrophy of variable severity, and swelling or local heat in an occasional case of acute bursitis. In cases in which the shoulder joint is free of all of these signs, the primary cause of the trouble usually is elsewhere.

Whenever shoulder and arm pain is considered, it must be remembered that a number of lesions of the chest may cause this pain also. Of these I shall mention cardiac pain which may be referred to the arm first. According to Smith the most important feature of such pain is that it must be produced by effort. It occurs during effort and not afterward.

Lesions of the superior pulmonary sulcus adjacent to the brachial plexus or sympathetic chain also may cause pain of the arm. Pancoast described a syndrome including roentgenographic shadows of the tumor at the apex of the lung, a neuritic type of pain of the arm, atrophy of the muscles of the hand and arm, and Horner's syndrome. This syndrome is not a distinct clinical entity since neurofibromas or inflammatory lesions as well as malignant lesions may cause it. Pain from lesions of the esophagus is rarely referred to the arm. Diaphragmatic lesions, however, may cause pain in the arm. This is particularly true of lesions of the central portion of the diaphragm, such as esophageal hiatal hernias. Diaphragmatic pleurisy also may cause pain in the shoulder and arm.

CARTILAGINOUS TUMORS OF THE HAND*

JOHN G. SHELLITO AND MALCOLM B. DOCKERTY

Cartilaginous tumors of the hand, on the basis of pathology, may be divided into two types: enchondroma and ecchondroma. The synonym for enchondroma is chondroma. Ecchondroma is called "perichondroma," "osteochondroma" and "exostosis." (The word "osteochondroma" is restricted to the ecchondroma.)

* Abstract of paper published in full in *Surgery, Gynecology and Obstetrics*, 86:463-472 (Apr.) 1948.

The fact that the entire group of cartilaginous tumors is commonly called osteochondroma has led, both in the past and in the present, to a great deal of confusion. It is better to use the terms enchondroma and echondroma.

Distinction between the two cannot be made with slide and microscope alone.

An enchondroma is usually a small cartilaginous tumor located centrally in the bone shaft, growing from many centers and expanding in all directions. Rate of incidence of pathologic fracture in our series was 26.6 per cent. The enchondroma occurs much more often in the hand than does the echondroma (3 : 1). These tumors, in comparison to normal hyaline cartilage, show increased vascularity, calcium deposition and myxomatous degeneration.

Two tumors of the tendon sheaths were found, both of which were enchondromas. In one of these cases multiple enchondromas of the sheath had developed and this is good evidence that an enchondroma can occur in the tendon sheath away from the site of tendon insertion.

The echondromas occur peripherally in bone near the end of the shaft and have a bony base and cartilaginous cap.

Either type of tumor may be malignant in which case it is usually a sarcoma. In this series 2 per cent were malignant. Both types are prone to recur although recurrence does not mean malignancy unless a mitotic figure can be found.

The treatment in both types is conservative operation.

THE COMBINED OPERATION FOR LOW BACK AND SCIATIC PAIN; A FOLLOW-UP STUDY*

H. HERMAN YOUNG AND A. CYRIL WALSH

Much has been written regarding the diagnosis and various methods of treatment of low back and sciatic pain but little has been written regarding end results. The criteria for making the diagnosis are now fairly well established and knowledge of these criteria has been widely disseminated. The operation for the removal of the protruded disk has been well standardized and knowledge of it is common among those surgeons who operate on patients who have the condition.

Considerable difference of opinion still exists as to the best method of treatment to be employed. It is safe to say that nearly all observers agree that the great majority of the patients are relieved of their symptoms by conservative treatment. A small number of the patients, perhaps 10 per cent, are not relieved by the usual conservative methods and surgical treatment is employed.

* Abridgment of paper submitted to the Archives of Surgery.

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CHOICE OF PROCEDURE

It is regarding the treatment of those who do not respond to conservative procedures that opinions vary as to the best method. At the clinic we believe that these differences of opinion, each seemingly justified by theoretic argument now, can only be reconciled after a large series of follow-up studies have been reported. It is with this in view that the present series is presented.

The so-called combined operation at the clinic includes the operation in which a member of the neurosurgical staff explores the spinal canal for evidence of an intraspinal lesion and removes it if one is found and that in which a bone grafting operation is performed immediately by a member of the orthopedic staff.

An orthopedic surgeon examines all patients with low back and sciatic pain before the decision to operate is made. The orthopedic surgeon, consulting the neurosurgeon, decides whether or not the combined operation should be performed. In some cases the roentgenogram reveals what is felt to represent an unstable spinal column and a bone grafting operation is advised. In other cases the decision is not made until operation when the stability can be tested.

INCIDENCE OF COMBINED OPERATION

Some idea of the frequency with which disks are removed or the combined operation is performed at the clinic can be gained by reviewing all cases of backache seen in one year. In the year 1940 there were 5,031 cases in which patients were examined because of the symptom, "backache." In this group the presence of a protruded intervertebral disk was suspected in 1,123 cases. Conservative treatment was advised in all but 422 of the 1,123 cases. In these 422 cases a protruded disk was removed surgically but the combined operation was performed in only forty-nine (12 per cent) of the 422 cases.

At first glance it would seem that if 422 of 1,123 patients were operated on for protruded intervertebral disk, then surgical treatment is given ultimately in 38 per cent of all cases in which presence of a protruded disk is suspected. The percentage in this group is much higher, we believe, than that in the general population. Since knowledge of the protruded disk syndrome has become widespread the diagnosis in many of our cases has been made by the patient's physician elsewhere and the patient is referred to the clinic for surgical treatment after he has failed to respond to the usual conservative measures. This influx of referred patients tends to color our statistical results. It would probably be more nearly accurate to say that 10 per cent of patients ultimately require surgical intervention for relief of pain associated with protruded intervertebral disk.

Since operations for protruded intervertebral disks have been performed in any number, the combined operation has been developed gradually. In 1936 and 1937 no spinal fusions were performed when a protruded disk was found and removed at the time of operation. In 1938 the combined procedure was carried out in 3 per cent of the cases and there has been a gradual yearly increase in the percentage until in both 1943 and 1944, the last years of the present study, 28 per cent of the patients who underwent operation for removal of an intervertebral disk also underwent spinal fusion.

These percentages are figured only on the basis of the number of cases in which a protruded disk was found and removed at the time of operation and do not include those in which an intraspinal lesion was not found at the time of exploratory operation but in which a bone grafting operation was performed.

Patients who underwent removal of a protruded intervertebral disk and, simultaneously, a bone grafting operation in the years 1941 through 1944 included those who had a narrowed interspace, those with a narrowed interspace and hypertrophic changes and those with partial sacralization of the last lumbar vertebra. In addition, there has been a small gradual increase in the number of patients who have recurrent symptoms of protruded intervertebral disk or actual recurrent protrusions and this has added some to the percentage of combined operations.

By far the greatest increase took place, however, in that group of patients who had a narrowed interspace at the site of the protruded disk. In the three years prior to 1941 a total of only thirty-eight patients who had a narrowed interspace underwent spinal fusion after a protruded disk had been removed. Starting in 1941 the number of patients in this group rapidly increased until in 1944 alone fifty-eight such patients underwent the combined procedure. Likewise the number of patients having a narrowed interspace plus localized hypertrophic changes increased from six in 1940 to forty-four in 1944.

Whether or not the finding of a narrowed interspace alone is a justifiable reason for the performance of a bone grafting operation is debatable. It seems only reasonable to assume that if sufficient cartilage extrudes from between two vertebrae the interspace will become narrowed. If the intervertebral disk has protruded only because of a degenerative process that is taking place in the disk itself then one may assume that this process is going to continue and lead to further narrowing of the interspace. With further narrowing the osteo-arthritis changes occur and the joint then becomes a source of pain and disability to the patient. We have observed that these changes take place in the unfused spinal columns of a few patients after the removal of protruded disks and believe that this is the reason why the number of patients having the combined operation in this group has increased. The fusion has been performed not only to relieve the symptoms present but also to help assure a long-term good result without a secondary operation. It is with the same purpose that the patient with a partially sacralized vertebra is advised to undergo spinal fusion. Few observers will deny the value of the bone graft when localized osteo-arthritis has developed in the lumbosacral joint. In general, the recommendation that a combined operation rather than the simple removal of the protruded disk be performed depends on the existence of a condition in the spinal column that in former years has been felt to be a cause of backache.

OPERATIVE AND POSTOPERATIVE TREATMENT

The combined operation as performed at the clinic is not the terrifying operation that advocates of "simple" laminectomy would lead one to believe. In order to avoid confusion in the operating room the orthopedic operating team usually waits until after the neurosurgical team has finished its part of the operation. The part of the spinal column to be fused is then

measured with a lead tape and a bone graft is removed from the tibia. This graft is divided into two pieces and these are used as a bilateral graft, one piece being placed in the prepared beds on each side of the spinous processes. The wounds are then closed and the patient is returned to bed.

At the end of three weeks the patient is allowed up and wears a high back lumbosacral type of belt for from six to nine months or until there is evidence of a solid fusion. The patient is advised to do no work for three months after the operation but at the end of that time he may engage in light work which does not necessitate bending, lifting or stooping. He is advised to avoid heavy work for one year after the operation. We feel that the allowance of some degree of muscular activity helps to stimulate the fusion.

As soon as the fusion is solid the belt is removed and a series of graduated exercises is started in order to re-establish muscular tone and strength. At this time the patient may experience some degree of pain and he is told that this is not unusual. If this explanation is not made he may be overly cautious in attempting to regain his normal activity and do more harm than good. Most orthopedic surgeons have observed patients who have become frightened by the pain and returned to bed and stayed for long periods. If they do, the grafts may absorb simply because of the disuse.

With this plan of rehabilitation we believe it is simpler, less costly and less time consuming to perform the fusion at the time the disk is removed in that group of cases in which it ultimately will be necessary to perform spinal fusion rather than to perform a second operation later.

Only one postoperative death occurred among the 526 patients who underwent combined operation during the years 1941 through 1944, a mortality rate of 0.2 per cent.

RESULTS

Judging the end results is a difficult undertaking because of the numerous factors involved. In each case it must of necessity rest on subjective rather than objective findings. Most patients who have a protruded disk complain of two pains: backache and sciatica. Judgment as to the amount of relief obtained must rest on both of these complaints rather than on either one separately. Results were considered to be excellent if the patient stated that he was completely relieved. Results were good if the patient obtained nearly complete relief but still continued to have mild backaches or even mild leg pains from time to time but was not incapacitated by these symptoms. If the patient received some degree of relief only, results were considered to be fair while if the patient was no better or even claimed to be worse after operation the result was considered to be poor. All patients in this series were examined at the clinic or were followed up by letter from one to five years after operation.

Of the 492 traced patients, 61 per cent claimed to have obtained excellent results while an additional 20 per cent obtained good results. Thus one could state that the result was satisfactory in a total of 81 per cent of the entire group. Twelve per cent of the results were fair and in 7 per cent of cases the result was judged to be poor.

In a separate study carried out at the clinic on 1,217 patients who had had a protruded disk removed during the years 1939 through 1941, Love

was able to ascertain the result in 987. In that group in which fusion was not performed 33.7 per cent of the patients were completely relieved while an additional 36.7 per cent obtained partial relief of the symptoms for which they underwent operation. Those thus benefited totaled 90.4 per cent, those not benefited totaled 9.6 per cent. When asked regarding their backs, 38.5 per cent of these patients answered that they had back pain and 34.5 per cent claimed to still have some leg pain. Of these 987 patients 64.4 per cent were able to return to their former occupation. In our present group, in which the male patients only were tabulated according to their ability to return to their former or a similar occupation a favorable reply was obtained in 71 per cent of the cases. Thirty of fifty-eight males in the present series who underwent the combined operation and failed to return to their former occupations were receiving compensation or insurance. This may or may not have been an influence. Thus, to compare these two groups, it may be noted that a somewhat higher percentage of patients who underwent combined operation obtained complete relief than of those who underwent simple removal of a disk and 6.6 per cent more were able to return to their former occupations.

Reports would seem to indicate that in the majority of the cases the simple removal of the disk will relieve the leg pain but that when the backache also is considered the results are not as satisfactory. When the combined operation has been used there has been a fairly uniform increase in the percentage of completely relieved patients. Thus if in some way it can be determined beforehand what patients ultimately will require spinal fusion for complete relief of their symptoms then the combined operation should improve the end results. It is impossible to even postulate what the end results at the clinic would have been had not this present group of cases been selected for a bone grafting operation to stabilize an unstable spinal column at the time of removal of the protruded disk. We feel that at least a large percentage of the now relieved patients would still be suffering from a backache of more or less degree.

NEGATIVE EXPLORATORY OPERATION AND BONE GRAFTING

There is one other group in which the combined operation is performed at the clinic. This is the group in which the presence of a protruded disk cannot be ruled out prior to operation. In these cases, no intraspinal lesion is found at the time of exploratory operation, but a bone grafting operation is performed. On the whole this group comprises a more difficult series of patients to treat and one does not expect the results to be as good as in the other series. The percentage of satisfactory results in this group was 74 per cent if the excellent and good results are combined. However, poor results were obtained in 15 per cent of cases in this series as compared to 7 per cent in the previous group. Nevertheless, 74 per cent of the males in this series were able to return to their previous occupation or one of a similar nature. Again, a compensation or insurance factor was present in eleven of the eighteen cases in which patients did not return to their former work. We feel that the results in this group have proved satisfactory enough to warrant a continuance of this procedure until a more suitable method of treatment can be adopted.

CUP ARTHROPLASTY OF THE HIP*

WILLIAM H. BICKEL AND FRANK S. BABH

A preliminary survey of the results of cup arthroplasty of the hip was made in November, 1944, in cases in which operation was performed at the Mayo Clinic from June, 1939, through December, 1942. Although the results in all cases were not all that could be desired, they were sufficiently encouraging to justify continued use of this operative procedure. At that time 111 operations performed on ninety-one patients were considered. From 1943 through 1945 cup arthroplasty was performed 163 times on 142 patients; this makes a total of 274 hips and 233 patients treated in this way from 1939 to 1945 inclusive. A complete follow-up of the entire group now has been made. No cases are included in this report in which operation was not done at least one year prior to the date of evaluation. All patients included have been heard from or examined within the past year.

PATHOLOGIC CONDITIONS

Although in many instances the cause of a distorted hip can be determined from the history and clinical and roentgenologic findings, this is not always possible. Degenerative disease of the hip, commonly known as *anatum coxae senilis*, embraces varied pathologic conditions, the onset of which may not be remembered or the symptoms from which may have been subclinical. Mild slipped femoral epiphysis, or Legg-Perthes' disease, congenitally shallow acetabula and other conditions would fall into this group. Posttraumatic hypertrophic changes are difficult to distinguish from the changes due to "osteo-arthritis of the hip."

SELECTION OF CASES

With few exceptions patients who were advised to have cup arthroplasties at the clinic were having sufficient pain so that they demanded operative interference for its relief. In some cases the fixed deformity alone was sufficient to require correction. In cases in which both hips were affected, the surgeon had no choice except to perform cup arthroplasty in an attempt to obtain at least one movable hip.

Many patients who felt they were having sufficient distress to warrant an operation were advised to pursue a course of conservative treatment. This consisted of limited activity, reduction of weight, use of a cane or crutch, physical therapy and the taking of aspirin. Aged patients and those whose distress was not too severe in the eyes of the examining physician were included in this group. Some additional patients were advised to continue conservative treatment because medical examinations indicated that the risk of this operative procedure was great for them.

Patients who had unilateral disease of the hip and whose occupation required heavy manual labor were advised to have arthrodesis of the hip rather than cup arthroplasty. A few patients absolutely refused to permit arthrodesis of the hip. The possibility of a failure after cup arthroplasty was discussed with these patients, and they were advised that arthrodesis could be carried out if cup arthroplasty failed.

* Abridgment of paper published in full in the *Journal of Bone and Joint Surgery*, 30-A: 647-656 (July) 1948.

Aged persons who were *not in good condition* were excluded from the operative group. The physiologic age appeared to be less than the chronologic age for most of the patients who were in the age group from sixty to sixty-nine years. *Included also were a few adolescent patients who presented such severe conditions that operative treatment was necessary.* Full growth should be obtained if possible before cup arthroplasty is undertaken. One of the patients in our series who was only twelve years of age presented a difficult problem because of aplastic congenitally dislocated hips. Arthroplasty for which a lucite cup was employed was performed and the result, four years after operation, was good.

SURGICAL TREATMENT

No special immediate preoperative preparation is necessary in these cases. Patients who are greatly overweight are forced to reduce before cup arthroplasty is undertaken.

No detailed description of the operative technic is indicated, for, in the main, that advocated by Smith-Petersen was employed. Various modifications were made as dictated by the individual case and the desires of the surgeon.

When the acetabulum was too shallow for the cup, it was either reamed out to allow room for a freely movable cup or supplemented by a shelf to make it sufficient. In cases in which ankylosis was nearly complete and a deep acetabulum was present a portion of the head of the femur was left in the acetabulum to make it more shallow. Radical acetabuloplasty was done in some instances so that the cup did not sink within the rim of the acetabulum. This procedure was employed most frequently in cases of arthrokataclasis. The head of the femur was always trimmed sufficiently to allow the cup to move freely on it.

From the roentgenograms it was obvious that in some cases the hips were unsuitable mechanically for a routine cup arthroplasty. The head of the femur was small and the neck short or there was a severe distortion of the neck. Early in experience some attempts were made to perform cup arthroplasty on such hips with poor results. Now a more extensive reconstruction, such as a Whitman operation or a Colonna operation supplemented by a cup, is done.

After operation a Hodgen splint was applied with moleskin traction on the leg to hold it in internal rotation and abduction until the wound was healed. This usually took twelve to fourteen days. An arthroplasty splint was then applied. The patient usually indicated when he felt able to be about on crutches. Most frequently he was able to do this in a little less than three weeks after operation. Some but not all of the patients were given physical therapy. In four to six weeks the patients were usually allowed to go home.

The time at which weight bearing was allowed depended somewhat on how extensively the head of the femur was remodeled. If considerable cortical bone was left, full weight bearing was allowed early. When it was necessary to trim the head down to cancellous bone, more time was allowed for healing and reorganization of this surface before full weight bearing was permitted. Usually a period of four to six months was recommended.

POSTOPERATIVE COMPLICATIONS

Infections in the wound occurred in ten cases. Three of these infections were inconsequential and superficial. The end results were good in two of these three cases and poor in one case. In two instances the infections were deep, but the wounds subsequently healed with the cups in place. The end results in these two cases were poor. In five cases drainage continued until the cups were removed; the end results were poor in four cases and fair in one case. In one of this last group the infection was felt to be blood borne, since drainage did not appear until five months after operation. Drainage was still occurring four years after operation. Thrombophlebitis developed in one case after operation.

In three patients dislocation of the cups occurred: One was replaced surgically two weeks after operation and a very good result was obtained. One was replaced by manipulation under anesthesia, but the final result was poor enough so that arthrodesis was done later. In the third case further operation was performed elsewhere because of the poor result. In several cases the position of the cup was poor and manipulations were carried out postoperatively because of the bad position of the cup with successful repositioning.

Excessive proliferation of bone about the cup and hip occurred in two cases in which the disease was unilateral and ankylosis recurred in both hips in a case of rheumatoid arthritis. If late postoperative roentgenograms could be obtained in all cases, it is felt that bony proliferation about the cup might account for some of the poor results which have not been explained.

A rather unique and unclassifiable group of cases were those in which vitallium cup arthroplasty was employed without success and the cup then was removed and not replaced. In one case of unilateral disease in which this occurred a good result was obtained. In two cases in which bilateral operations had been performed the cups were removed and a Colonna type of pseudarthrosis was established. In both of these cases hips had been ankylosed at 90 degrees flexion. Even though the patients walked with canes the end result was considered good because of the severe preoperative disability and the fact that the patients seemed well satisfied with the result. One patient who had undergone bilateral operations in which vitallium cups were inserted had one cup removed without any replacement. The result continued to be poor. A second arthroplasty in which a vitallium cup was used was done in two cases after the head of the femur had been remodeled. Good results were obtained.

In five cases of unilateral disease fractured lucite cups were removed operatively. In cases of bilateral disease six fractured lucite cups were removed. Secondary procedures carried out on these patients were simple removal, replacement with vitallium cups and arthrodesis. End results varied. In four additional cases in which lucite cup arthroplasty was employed, the cups probably have been fractured but exploratory operation has not been carried out.

In one case the femur was fractured during the attempt to dislocate the hip at operation. Union was obtained and later vitallium cup arthroplasty was done with a fair result.

RESULTS

The result was considered to be very good when the patient had no pain, could walk up and down stairs, tie his shoes, and walk without assistance and without a noticeable limp. A good result was considered to have been obtained when the patient had little or no pain, could walk up and down stairs, and could walk without assistance or with the assistance of a cane.

Patients were considered to have a fair result when they were satisfied that improvement had been obtained. Pain sometimes persisted but it was less severe than before operation and was bearable. Motion may or may not have been improved. Many patients still used a cane or a crutch. Frequently deformity and grossly abnormal gaits were improved but some disability persisted.

The poor results were those in which the condition was not improved by the procedure and the patient was not satisfied. Only a few patients felt that they were made worse by the operation. The greatest percentage of good and very good results was obtained among patients of middle age with a tapering off toward the younger and older ages. Apparently there is little sex preference; if anything the females did slightly better than the males. This may perhaps be explained by the fact that males use their hips for heavier work than do females.

COMMENT

Detailed analysis of these cases revealed that patients should be selected carefully for cup arthroplasty on the basis of (1) physiologic age, (2) temperament and ability to co-operate, (3) reconstructive possibilities of hip as analyzed from roentgenograms, (4) muscle power and (5) occupation.

All patients should be acquainted with the possibilities of failure and success and the alternate operations should be discussed with them. In cases of disease of both hips or in cases in which degeneration of the opposite hip is expected there is no alternative. Drilling operations, cheilotomy, fascial arthroplasty and others have not stood the test of time. Osteotomy to change the weight bearing surfaces of an already incongruous and worn-out joint does not seem reasonable. Neurectomy of the obturator nerve may help. It has not proved of great help in relieving persistent pain following cup arthroplasty; in our hands, however, the number of cases in which it has been done is not great.

Prostigmine has been used after operation in some cases to relieve muscle spasm and pain. The results were not too encouraging although several patients felt it helped considerably. Curare has been used in conjunction with physical therapy in a few cases to obtain muscle relaxation with equivocal results thus far.

Some of the best results obtained have been in cases in which the degenerative process or mechanical irregularity of the head of the femur was in the formative stage and the acetabulum was involved only mildly. It is difficult to advise early operation for a patient who has distortion of the hip joint but is not having much pain, although one knows that ultimately the hip will break down. Perhaps in these cases cup arthroplasties should be done before secondary osteo-arthritis develops.

Comparison of the results recorded in the eighty-eight cases in which cup arthroplasty was carried out at the clinic prior to January, 1943 with

16 per cent in the case of lesions of the medial semilunar cartilage and 13 per cent in the case of lesions of the lateral semilunar cartilage. This higher percentage of accurate diagnosis in series 2 is the result of increased experience gained by the careful taking of histories and more careful recording of our observations made at operation. It is our opinion that a carefully taken history contributes more to a correct diagnosis than do all of the special tests and roentgenograms. It must be remembered that the diagnosis is concerned with subjective symptoms, and that many patients do

TABLE 2

OPERATION, PATIENTS, TYPE OF INJURY:
 LESIONS OF THE SEMILUNAR CARTILAGE (SERIES 2), 1934 THROUGH 1944

Operation, patients, lesions	semilunar cartilage					
	Medial or lateral		Medial only		Lateral only	
	Number	Per cent	Number	Per cent	Number	Per cent
Arthrotomy	321		263		56	
Patients	318		268		50	
Total tears	253	78.8	214	80.8	39	69.6
Bucket-handle	122	48.2	109	50.9	13	33.3
Anterior one third	40	15.3	32	15.0	8	20.5
Medial one third	16	6.3	15	7.0	1	2.6
Posterior one third	44	17.4	36	16.8	8	20.5
Multiple	5	2.0	3	1.4	2	5.1
Unclassified	26	10.3	19	8.9	7	17.9
Associated demonstrable injury, ligaments	12	4.8				
Associated demonstrable injury, patella	8	3.2				

not tell their stories well. Hence, great patience must be exercised by the surgeon in questioning them.

The commonest type of fracture of these cartilages encountered in series 2 was the bucket-handle type, so named by Sir Rutherford Morison because of the morphologic similarity of the lesion to the leather bucket handles of pails used in mines. The preponderance of this type of fracture in series 2 agrees with the figures of most other writers on the subject, who have reported that about 50 per cent of fractures of the semilunar cartilage were of the bucket-handle variety. The frequency of occurrence of the

tears in other parts of the cartilage in series 2 can be seen in table 2. It would seem, by analysis of this table, that on inspection of the joint through an anterior incision it would be quickly discernible that there was a definite tear of that portion of the cartilage which was visualized in about three fourths of the cases in which a pathologic process was found.

In the second series of cases three patients had tears of the medial semilunar cartilages in both knees, and one patient had tears of both the medial and lateral cartilages of the same knee. There were sixty-eight (21.2 per cent) cases in which arthrotomy was performed without definite demonstration of a tear in the meniscus. In many of these cases it was noted that fibrillated cartilages, loose cartilages or hypertrophied fat pads were present. However, when observations such as these represent the only pathologic processes noted, we are likely to look on such diagnoses with suspicion.

TABLE 3

RESULTS OF ARTHROTOMY FOR TEARS OF SEMILUNAR CARTILAGES (SERIES 2)

Operations, patients, results	Semilunar cartilage					
	Medial or lateral		Medial only		Lateral only	
	Number	Per cent	Number	Per cent	Number	Per cent
Arthrotomy, total	341		263		50	
Patients, total	318		262		50	
Known results, total	284	88.5	233	88.7	49	87.5
Excellent	220	77.5	187	79.6	33	67.3
Improved	47	16.5	35	14.9	12	24.5
Not improved	17	6.0	13	5.5	4	8.2

We feel that the pathologic processes noted in the majority of such cases do not account for the symptoms. Of the sixty-eight cases in which arthrotomy was performed and in which no definite tear was demonstrated, a cyst of the lateral cartilage was found in four and a cyst of the medial cartilage was found in one. A discoid lateral cartilage was found in two cases; in two other cases the cartilage was thought to be congenitally abnormal and approaching the discoid type. There was a tear of the anterior cruciate ligament in two of these cases and of the plica alaris in one; in all three of these the locking or catching which the patients described was thought to result from the laxness of the joint. In the 253 instances in which definite tears of a cartilage were demonstrated at the time of operation, definite injury to ligaments was visible in twelve (4.8 per cent) and injuries to a patella were visible in eight (3.2 per cent). More will be said about these observations later in this paper.

In the 321 cases in which arthrotomy was performed in series 2, follow-up reports were available in 284 (88.5 per cent). The time interval after surgery was a minimum of six months, but in most cases it was longer. If the patient said that he had a normal knee which allowed him to carry on his usual activities without pain, swelling, stiffness, locking or instability, his condition was classified as being "excellent." If the patient felt that his knee was better than before surgical treatment, but if the patient still had pain, swelling or stiffness which were not so severe as seriously to limit his occupational activities, his condition was classified as "improved." If the patient felt that the knee was no better, or was worse than before surgical treatment, his result was listed as "not improved." In table 3 are shown the over-all results obtained in series 2, and in table 4 the results between the two series are compared. It can be readily seen that the results in the two series were closely parallel.

Normal functioning knees were obtained by 77.3 per cent of our traced patients after surgical treatment (table 4). The thought naturally arises

TABLE 4

RESULTS OF ARTHROTOMY FOR TEARS OF SEMILUNAR CARILLAGES (SERIES 1 AND 2)

Series	Total patients traced		Results					
	Number	Per cent	Excellent		Improved		Not improved	
			Number	Per cent	Number	Per cent	Number	Per cent
1 . . .	320	94.9	247	77.2	40	14.4	27	8.4
2 . . .	284	89.3	220	77.5	47	16.6	17	6.0
Total	604	92.2	467	77.3	93	15.4	44	7.3

as to why the other 22.7 per cent of patients did not likewise obtain good results. As we have already pointed out, there were sixty-eight cases in which arthrotomy was performed in series 2 in which no meniscal tear was present, although a fair number of the joints surgically explored did have other pathologic processes which were definite. In this group in which arthrotomy was carried out sixty-eight times, only thirty-four patients (50 per cent) were cured by the surgical treatment. Among the cases in which arthrotomy was performed 253 times, and in which definite tears of cartilage were seen, an associated tear of one of the cruciate ligaments was noted at operation in ten cases and a tear of the internal collateral ligament in two cases. In these twelve cases only six (50 per cent) of the patients obtained complete relief. In another eight cases there was an associated injury of the patella in the form of chondromalacia or osteochondritis dissecans of the patella. It is probable that these two conditions are only variables of

the same pathologic process. At any rate, both probably are the results, in most instances, of direct trauma. Of these eight patients who had an associated injury of the patella only two (25 per cent) obtained a good result. Three of the seventeen patients of the entire series whose condition was not improved were from this group of eight. Soto-Hall found twelve cases (18.5 per cent) of traumatic degeneration of the articular cartilage of the patella in sixty-five cases in which arthrotomy was performed in a military hospital for chronic conditions of the knee. Cave and associates found the same condition in nine cases (7 per cent) of 124 in which arthrotomy of the knee was performed consecutively in another military hospital. In our cases, the associated lesions of the patella at the time were thought to be incidental, but it is open to question whether they were not actually as important as, if not more important than, the injuries to the cartilages. The same probably is true in respect to the associated injuries to ligaments.

We have also learned that some of our patients who were not satisfied with the results of surgical treatment reported that although their condition was improved, they were not freed of all difficulty with the knee. Some of them, on close questioning and at examination, said that locking of the knee joint was relieved, but that the weakness was not helped. Many of these patients had torn anterior cruciate ligaments that allowed a slipping forward of the tibia. We did not recognize this before operation, and did not tell the patient that our operation would relieve only the locking. In these cases the weak anterior cruciate ligament was not weakened sufficiently to warrant performance of any of the recognized operations for instability of the knee. Perhaps not until recent years has the importance of a strong quadriceps mechanism as means of relieving some of the instability of which patients complain been stressed strongly enough.

Had we been especially vigilant to detect these conditions in all cases, it is probable that more would have been noted. The question arises, therefore, as to whether, instead of the routine 2 inch (5.08 cm.) incision through which most surgeons remove the semilunar cartilage, it would not be wiser to use a longer incision and thereby to gain wider exposure of the joint, so that the ligaments and undersurface of the patella could be inspected in all instances. We believe that the explanation for many of the 22.7 per cent of patients in both series 1 and series 2 who were not cured (table 4) lies in a consideration of the factors we have just mentioned, and not in whether a part or all of the cartilage was removed.

It has been the practice of most of the orthopedic surgeons at the Mayo Clinic to remove only that portion of the meniscus which was torn; this has been especially true in the case of bucket-handle tears. In the majority of bucket-handle tears only that portion of the cartilage which could be excised through the anterior incision has been removed. If, however, a tear of the posterior third of the meniscus is suspected and if no tear is visualized through the anterior incision but the history is strongly indicative of a torn cartilage, then probably the entire cartilage should be removed. We feel that this procedure can be accomplished more easily and safely by the use of a posteromedial or posterolateral incision to remove the posterior portion of the meniscus.

Although most British and many American writers now advocate that the entire cartilage including its peripheral attachment be excised in all

instances, we feel that such a procedure probably makes little difference in the results. We do not advise routine removal of the entire meniscus. In our cases in series 2 in which there was a definite tear of the internal meniscus, the entire cartilage was removed in 22 per cent of the cases. The torn portion and in many instances only the anterior two thirds or four fifths of this portion were removed in 78 per cent of the cases. The good results (77.3 per cent) in those cases in which the entire cartilage was removed were the same as for the series as a whole.

The only postoperative infection of consequence occurred in a patient whose entire semilunar cartilage was removed; ankylosis of the knee ultimately resulted in this case. It is generally acknowledged by surgeons of large experience that the incidence of infection of wounds increases in direct proportion to (1) the length of time the wound is open, (2) the length of time the tissues are exposed to the air and (3) the trauma incident to the operation. When the entire meniscus is removed the operating time generally is prolonged and considerable trauma is inflicted on the joint. Moreover, hemorrhage into the joint is definitely increased and as a result of this alone the convalescent time is likely to be increased. In view of these facts and our results, we feel that in the majority of cases the surgeon is not justified in making a difficult and prolonged procedure out of one which can be carried out easily within a few minutes with a minimum of trauma, hemorrhage and postoperative reaction. If the surgeon feels that entire removal of the cartilage is indicated, we believe this can be accomplished by the average surgeon with the least trauma through two incisions. There may be a few skilled surgeons who can, with special instruments, satisfactorily remove the entire cartilage through one incision, but we are sure this does not apply to the average surgeon who performs surgery of the knee joint.

SUMMARY AND CONCLUSIONS

The cases in which arthrotomy of the knee has been performed at the Mayo Clinic for derangements of menisci through 1944 have been reviewed. This procedure has been carried out 664 times for 635 patients who had the condition in question.

The diagnosis of meniscal injuries or abnormalities can be established best by the careful taking of a history in which locking of the knee joint followed by pain and swelling is elicited. This triad was present in 70 per cent of our cases.

In many cases of injury to the menisci there are associated injuries of the ligaments or of the articulating surface of the patella. In this group of patients the results of surgical treatment are likely to be considerably worse than among those patients whose injury is confined to the semilunar cartilages.

The results of excision of the torn portion of the cartilage and the results of excision of the entire cartilage were essentially the same in the more recent of the two series of cases concerned herein.

HEREDOFAMILIAL CLEFT FOOT DEFORMITY (LOBSTER-CLAW FOOT OR SPLIT FOOT)*

HENRY W. MEYERDING AND JACKSON E. UPSHAW

Cleft foot, sometimes known as "lobster-claw foot" or "split foot," is a rare congenital deformity which has a definite tendency toward hereditary transmission. There are many variations of the deformity, and an exact or uniform description of it cannot be given, but the following general statements may be made. The usual deformity is one in which a cleft occurs at the second or third digit and extends a variable distance up the forefoot, perhaps involving even the tarsus, and is associated with a defect or absence of bones in proximity to the cleft. The portions to either side of the cleft are molded into a somewhat conical form, usually terminating in distorted joints and giving an appearance not unlike that of a lobster claw. Grand and Dolan in 1936 reviewed the extant literature on cleft foot, reported three cases of their own and believed that all four extremities show the deformity, that the hands are never defective in the absence of the deformity of the foot, nor is one foot ever deformed alone. The variations in the degree of the defect are many and may involve from one to four toes, occasionally including the tarsus. The digits most commonly affected are those adjacent to the cleft. The first and fifth toes in the majority of cases escape. It is an invariable rule that the proximal bone is never absent when a corresponding distal one is present. Of the metacarpal bones which remain, those bearing terminal phalanges are usually considerably thickened, while those which have no phalanges show hypoplasia.

In our review of the literature through 1943 and in study of our cases, we have found nothing in conflict with the statements of Grand and Dolan. The deformities of the hand which accompany cleft foot are extremely variable, they include hands with webbed fingers, long thumbs, no thumbs, crooked thumbs, no fingernails, cleft fingernails, small fingernails and missing fingers.

The etiology of cleft foot and deformities of the hand has been made the subject of study by many geneticists. Recorded in the literature are many instances in which cleft-foot anomalies have been traced through several generations. The cleft-foot anomaly may be explained as a mendelian dominant character in which the distribution and ratio of the affected and unaffected persons is in accord with a single gene interpretation. The hereditary character is assumed to be completely dominant over the normal condition. More males than females are affected, but there is not sufficient evidence to warrant consideration of the character as a sex-linked, sex-influenced or sex-limited trait.

Before an attempt is made to treat these cleft-foot anomalies for correction of deformity and to improve function, it is necessary to have roentgenograms made in at least two planes in order to determine the exact bony structure present. The mere suturing of soft tissues after excision of the cleft may result in failure. In the feet proper, weight-bearing is essential, and to obtain this, osteotomy or excision of bone usually is required

* From the American Journal of Surgery, 74: 589-592 (Dec.) 1947.

for permanent results. Care in preservation of the blood supply to the remaining digits is necessary, for in these conditions the blood supply to the digits often is anomalous. The postoperative dressings must be carefully applied to allow for swelling. The circulation of the digits should be observed frequently after operation and, on the first evidence of impaired circulation, the dressings should be loosened. The first indications of impaired circulation usually are pain and swelling, followed by cyanosis,



Fig 83.—Left foot, showing: a, marked hallux valgus and flexion deformity with bunion over the left great toe; b, congenital fusion of the first metatarsal bone with the internal cuneiform bone; c, congenital fusion of the cuboid, middle and external cuneiform and navicular bones; d, distal articulation of the fourth and fifth metatarsal bones with the middle phalanx of the fifth toe. This drawing shows the actual fusion found at operation.

with cold, clammy, sweaty digits. Elevation of the foot postoperatively will aid in keeping swelling to a minimum. The retentive dressing, plaster of paris casts or splints which maintain the corrected position resulting from surgery must be kept on until the bony parts have become firmly united. The use of specially built shoes postoperatively often is required. In some cases in which the deformity is not severe, specially built shoes may be all that is required.

The following case illustrates the cleft-foot deformity and its surgical correction.

REPORT OF A CASE

A white boy fifteen years old was admitted to the Mayo Clinic on June 20, 1946. He had been born with a congenital bilateral lobster-foot deformity in which there was a cleft of the forefoot between the first and fourth metatarsal bones, with congenital absence of intervening structures. There was also a congenital web between the third and fourth fingers of the left hand. When the patient was six years of age the clefts of the forefeet had been partially closed by a simple plastic procedure, performed elsewhere, without any bony reconstruction. The

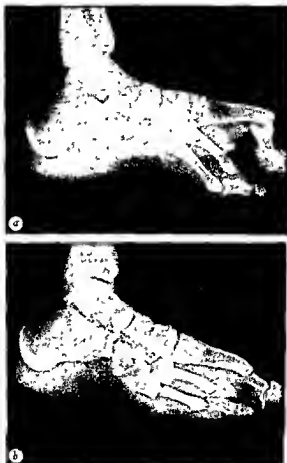


Fig 84a—Preoperative lateral roentgenograms; b, postoperative view of the same foot. The rudimentary joints appearing in these roentgenograms do not show the extent of fusion found at operation.

boy had been able to walk well and had suffered no pain in the feet until he was fourteen years of age. At this time he had begun to experience some pain from a "bunson" over the medial aspect of the head of the first metatarsal bone of the left foot. Accordingly, in the spring of 1945, a "bunionectomy" was performed elsewhere. After the operation marked hallux valgus deformity developed on the left, with a painful bunion. The deformity of the great toe forced the patient to walk on the lateral aspect of the foot, holding the foot in some degree of inversion. The marked hallux valgus deformity of the left foot, with its accompanying painful bunion and fixed inversion of the foot on walking, occasioned the patient's visit to the clinic

Physical examination revealed congenital absence of the second and third metatarsal bones and the second, third and fourth toes in each foot, with a cleft in the skin between the first and fourth metatarsal bones. Old operative scars at the base of the cleft indicated where the proximal aspect of the clefts had been closed previously. Hallux valgus was not present on the right, and the foot exhibited no eversion or inversion on weight-bearing. Marked hallux valgus with a bunion over the medial aspect of the head of the first metatarsal bone was present on the left (fig. 83). The nature of the hallux valgus deformity was such as to cause dorsal deviation of the first metatarsal bone and inversion of the foot on walking. Slight varus of the forefoot also was present. Scars were present between the third and fourth fingers of the left hand as a result of operative procedures carried out elsewhere to separate a congenital web between these two fingers. Function was normal in the fingers, except for slight limitation of extension of the third finger. The remainder of the general physical examination yielded negative results.

Röntgenograms of the feet (fig. 84a) revealed a congenital absence of the second and third metatarsal bones and phalanges of the second, third and fourth digits bilaterally. Congenital fusion of the navicular bone with the cuboid and middle and external cuneiform bones and the internal cuneiform bone with the first metatarsal bone was seen bilaterally. Rudimentary joints could be seen in the roentgenograms outlining the joints about the cuneiform bones but on examination they were found to be fused. On the left, marked hallux valgus with medial and partial plantar dislocation of the proximal phalanx was seen. Results of roentgenograms of the thorax were negative. Routine examinations of the blood and urine revealed nothing abnormal, and serologic examination gave negative results.

On July 2, 1946, osteotomy was carried out on the fourth and fifth metatarsal bones. About three fourths of an inch (1.9 cm.) of the fourth metatarsal bone was excised; this permitted the deformed lateral portion of the foot and fifth toe to be brought medially and somewhat dorsally. About three fourths of the proximal phalanx of the great toe was resected and heavy scar tissue was removed to allow swinging of the great toe from its 80 degree lateral deformity into proper alignment forward. A dimple on the ball of the foot and a scar from the previous operative incision were excised to facilitate approximation of the lateral and medial portions of the foot. The patient preferred not to have the right foot operated on at this time.

On the ninth postoperative day a cast extending from the toes to the knee was applied, and the patient was permitted to be up on crutches and to return home. On August 8, 1946, five weeks postoperatively, the patient returned for re-examination. The cast was removed and the wounds were found to be healed. There were a much improved weight-bearing surface and a more normal appearing foot than existed prior to operation (fig. 84b).

The patient returned to the clinic on July 7, 1947, for operation on the right foot, for he was very much pleased with the benefit derived from the operation on the left foot. Hence, a similar operation was performed on the right foot, after which a cast was applied. The cast was removed at the end of three weeks, at which time the wounds had healed, with primary intention. The stitches were removed and the patient returned home on July 30, 1947, with instructions to wear a cast, which we applied, for three months.

BONE AND JOINT CHANGES IN HEMOPHILIA WITH REPORT OF CASES OF SO-CALLED HEMOPHILIC PSEUDOTUMOR*

RALPH K. GHORMLEY AND REED S. CLEGG

The changes seen in joints of persons affected by hemophilia are quite familiar to the medical profession. In addition changes may be seen in the shafts of long bones in some cases of hemophilia. Such changes are much less frequently seen than are the joint changes and, in our experience, are more severe and result in disaster in most instances. Various authors have stated their opinion regarding the frequency of joint changes in hemophilia. Lyon-Smith reported that in 70 per cent of his hemophilic patients hemar-

* Abridgment of paper published in full in the *Journal of Bone and Joint Surgery*, 29: 41-52 (July) 1947.

throsis developed before the age of two years. In more than 78 per cent of the patients followed by Thomas joint symptoms developed usually in childhood and in some of the remainder the joints were affected later. In a series of seventy-six patients with hemophilia examined at the Mayo Clinic, forty-four, or 58 per cent, showed definite evidence of pathologic changes in the bones or joints. (There were in the files 150 cases in which a diagnosis of hemophilia had been made in the years 1920 to 1939 inclusive. Each patient in this series was graded 1, 2, or 3 on the basis of (a) history

TABLE 1

PRIMARY JOINT INVOLVEMENT IN FORTY-FOUR CASES OF HEMOPHILIA IN WHICH BONE AND JOINT CHANGES OCCURRED

Knee (right 15, left 8)	23
Ankle	6
Elbow	4
Hip	3
Wrist	1
Patella	1
Phalanx	1
Not given	3
Total	44

of hemophilia among relatives and (b) clinical and laboratory evidence of hemophilia. Only those patients with ratings of 2 or 3, that is, those with definite evidence of hemophilia, are included in this series.)

All of the forty-four patients in our series in whom pathologic changes developed in the bones and joints were males. The average age of these patients was 17.3 years. When first seen here thirteen patients were younger than ten years; twelve from ten through nineteen years; ten, from twenty through twenty-nine; five, from thirty through thirty-nine and four, from

TABLE 2

FREQUENCY OF JOINT INVOLVEMENT IN FORTY-FOUR CASES OF HEMOPHILIA IN WHICH BONE AND JOINT CHANGES OCCURRED

Knee	45*
Elbow	28
Ankle	26
Hand	13
Hip	8
Wrist	5
Patella	4
Phalanx	3
Sacral spine	1

* In some cases both knees were involved

forty through forty-nine. The average age is fairly high because the majority of these patients presented themselves during the chronic stages for treatment of complications. The known age of onset of hemarthrosis ranged between four months and thirty-five years, with the average being about seven and a half years.

Table 1 shows the joints first involved in thirty-nine of the forty-four patients and table 2 shows the comparative frequency of involvement of the individual joints. It is obvious that in our series weight-bearing joints

were more frequently involved than nonweight-bearing joints, and the knee was involved about twice as often as any other joint. Of the forty-four patients with hemarthrosis ten, or 23 per cent, had single joints involved while 34, or 77 per cent, had multiple joints involved.

In this group of cases were included six patients with unusual bone changes, five of whom were known to have hemophilia and one of whom had some type of blood dyscrasia or hemorrhagic diathesis which was never positively diagnosed. The extensive changes found in joints are familiar to those persons who are interested in hemophilia but our experience has led us to believe that the bone changes such as are seen in these cases are much less frequently seen and are less familiar to all interested in the disease than are the changes in the joints. Previous reports in the literature of cases in which there were extensive bone changes similar to those we are about to report are as follows.

Starker is credited by Echternaecht with being the first to describe such a lesion. In Starker's case of hemophilia a large tumor of the right thigh had developed; this was probed and a considerable amount of blood was evacuated. The patient died ten days later and the following is from the postmortem notes, quoted by Echternaecht: "Erosion of the cortex and spongiosa beneath an hematoma at the lower end of the femur. Calcified connective tissue strands extended from the cortex to the elevated periosteum on the anterior surface. No evidence of neoplasm was seen histologically."

Reinecke and Wohlwill reported a case in which there were extensive subperiosteal hemorrhages in a man, aged twenty-seven years, with hemorrhage into the knee. The disease ran a variable course but the patient died after three months in the hospital. A very complete report of the postmortem findings was given. Roentgenograms showed erosion of the bone "as seen in cases of aneurysm against vertebrae or sternum." The diagnosis at necropsy was: "Hemarthrosis of the right knee. Bone erosion on the medial condyle of the femur and tibia, new and old subperiosteal bleedings, anemia, acute lung emphysema. Streptococcemia." An excerpt from the extensive description of the microscopic findings is as follows: "Surprising is the picture of the surface of the cortex. Here we see nowhere a continuous compact bony layer. At the upper and lower edge of the hematoma as well as where the periosteum is still attached and where it is lifted up by hematoma we find numerous bone spicules at times surrounded by osteoblasts, attached to the bone and between them cellular bone marrow, here and there still containing some pigment cells. The border between this new bone formation and the old cortex is not a smooth surface, but the spongy spicules are attached irregularly to the cortex and also irregularly enter cellular marrow spaces into the cortex.

"In the region in which the hematoma lies directly on the bone one can see how the blood, or rather the granulation tissue formed from the blood has perforated the surface of the bone and entered into it. A few bone fragments have been separated by this process entirely and become necrotic. Around these lost fragments as well as the ones still connected with the cortex one finds giant cells with lacuna formation by erosion."

Firor and Woodhall presented a case of a white boy, sixteen years old,

* Translation by Dr. A. R. Pila.

with pain and swelling of the right thumb of eighteen months' duration which they believed "to represent the end stage of a traumatic hemarthrosis of hemophilic origin in a small articulation."

Becker reported two cases of "so-called resorption tumors" which he also called "hemophilic pseudotumors." One of these lesions had afflicted a fifty-one year old man of a family known to have a tendency to hemorrhage. A few years previous he had received a kick in the thigh by a horse. This had been followed by the development of a large hematoma. Within nine months a tumor appeared and enlarged slowly. Exploratory operation was performed. A tumor was found involving the muscle and extending down to the femur. The patient died thirteen days postoperatively, of tetanus. The pathologist's report on the tissue was "proliferation of fibrous tissue containing blood pigment next to foreign body giant cells and granuloma formation around foci of hemoglobin as well as lipoid containing cells."* A second case involved a twenty-three year old man, known to be hemophilic, who had a gradual swelling of the thigh. Needle biopsy was followed by severe bleeding. The roentgenogram showed a well-defined radiopaque mass distal to the lesser trochanter. The cortex appeared to be ruptured, as would occur in periosteal sarcoma. Biopsy of a node from the inguinal region revealed many pigment-containing cells, but nothing else.

Echternacht reported the case of a white boy, thirteen years old, who was a known hemophiliac with a history of repeated hemorrhages into various joints. He was finally admitted with a painful swelling of the anterior surface of the left tibia just below the knee. This had followed a slight injury three months previous to admission. Roentgen therapy and transfusions failed to arrest the enlargement of the tumor and an exploratory operation revealed an extensive hematoma. No neoplastic tissue was found. Finally a disarticulation through the knee was performed and death ensued. The specimen showed "large subperiosteal hematoma with massive necrosis of the underlying bone and necrosis and infection of the overlying skin."

Among our six patients with unusual bone changes were one with involvement of the phalanges of the thumb, one with involvement of the olecranon and four with involvement of the femur. In each case the bone involvement was monostotic. In all cases the most nearly adjacent joint was involved to some extent and there may be a reasonable doubt as to whether the bone changes were secondary to hemorrhages within the joint or whether they were due to primary hemorrhages within the bone or in the subperiosteal tissue adjacent to the bone.

REPORT OF REPRESENTATIVE CASES

Case 1.—A white boy, aged nine years first registered at the clinic on January 21, 1932. The history was that four weeks previous to admission the patient had cut his right hand with a knife. The hand had been bandaged tightly but hemorrhages had occurred four times with the formation of hematomas in the palm of the hand. The patient was transfused four times. With transfusions and dressings, bleeding was controlled and the wound healed.

The patient returned in April, 1935. He had noticed a gradual enlargement of the right thumb over a period of eighteen months. A bluish discoloration had taken place (fig. 85). Roentgen therapy was given over the affected thumb. The patient again returned in June, 1937. There had been a gradual enlargement of the thumb. Examination revealed a thumb four or five times as large as a normal thumb with a bulbous swelling of the terminal phalanx

* Translation by Dr. A. R. Pils.

who apparently had had hemophilia and of three paternal half brothers who were non-bleeders. The mother had four brothers who were bleeders and all died of hemorrhages before the age of twenty-five years. The patient thought his maternal grandfather may have had hemophilia. The mother's sister's two sons had hemophilia and another sister had one son who was a bleeder. Five sisters of the mother had sons who were nonbleeders. The patient had one daughter and one son who were not bleeders.

At the first admission the patient gave a history of repeated hemorrhages from the gums, nose, and so forth, usually stopped by pressure. At that time the right knee was "stiff" but there was no history of trouble with the femur.

At the time of the patient's second admission in April, 1938, he was referred by a surgeon who stated that he had first seen the patient five months previously, after a fracture of the right femoral shaft. It was the opinion of the referring surgeon, as well as that of the patient, that the fracture was a combined traumatic and pathologic fracture. The roentgenograms

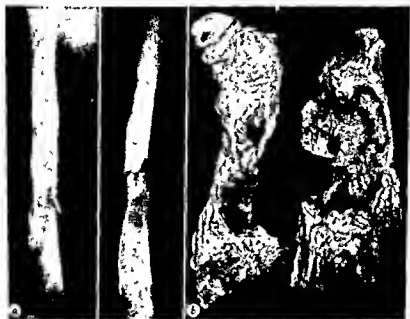


Fig 87 (case 2) *a*.—Anteroposterior and lateral views of the femur five months before admission in 1938. *b*. Anteroposterior and lateral views of the femur removed at necropsy. The bone was eroded extensively and surrounded by a mass of fibrous tissue.

showed an area of considerably lessened density of the shaft at the site of the fracture (fig 87*a*). A cast was applied for ten weeks but no callus developed and another cast was applied. After another interval of about the same time no evidence of callus formation was noted and there was evidence of actual erosion through the cortex. It was the opinion of the surgeon who referred the patient that the lesion "may have been due to areas of hemorrhage within the shaft." The patient gave a history of frequent intramuscular hemorrhages within the thigh.

The patient returned at intervals of from one to three months during the next four and one-half years. At each visit a transfusion was usually given, a cast was applied to the extremity from the groin to the ankle and over this a walking caliper brace was worn.

At the time of his last admission in November, 1942, the patient stated that he had been fairly well until two months before when something in the leg seemed to give way; since then he had had continual pain and he could feel the fragments of the femur grate together. Finally blood began to seep through the cast so he made a window in the cast and found an ulcer. He stopped work, received some plasma transfusions and finally the bleeding from the ulcer was controlled. Further bleeding took place and the patient received further transfusions of plasma. His general condition became worse and he felt weaker.

Examination on admission revealed two sinuses on the lateral side of the knee with foul-smelling discharge and blood coming from them. Roentgenograms revealed almost complete



Fig. 88 (case 3).—Small area of absorption in shaft of femur: *a*, lateral view; *b*, anteroposterior view. Erosion may be noted on medial side of femur.



Fig. 89 (case 3).—Specimen showing extensive hemorrhage into knee joint and into marrow cortex of femur.

destruction of the femur. Repeated transfusions were given but the patient grew progressively worse and died thirteen days after admission.

The following excerpts are from the protocol of the postmortem examination. "The right knee is ankylosed at 180 degrees. There is an ulcer measuring 8 by 4 cm. over the lateral aspect of the lower third of the right thigh. The margins are covered with necrotic tissue (fig. 87b).

"This ulcer communicates directly with a large cavity extending upward to the junction of the upper and middle thirds of the femur and downward toward the knee. The anterior and lateral walls of the femur in its lower two-thirds are absent . . . The marrow cavity is greatly expanded with thinning of the cortex in a number of places. It is estimated that there are about 1,000 c.c. of disintegrating clotted blood, apparently segregated in multiple loculi, particularly in the marrow cavity. The femur is fractured at the junction of the middle and lower thirds, but the fragments are held together by a few bands of fibrous tissue. The right knee joint is also filled with disintegrating blood clots.

"The section of the cyst wall shows a fibrous periosteum in which a few vessels are present. The underlying cortical bone is thin and in the marrow spaces normal bone marrow is replaced by loose connective tissue with numerous blood vessels . . .

"Section of the bone near the fracture shows numerous trabeculae of bone with fragmentation of bone spicules and intermixed with them areas of degenerating cartilage and solid masses of fibrous tissue, some of which is undergoing degeneration also. The marrow is hyperplastic, with a great increase in all cell lines."

Case 3.—A boy, ten years old, first registered at the clinic in 1928 complaining of pain and swelling of several joints for eight years. A second admission in 1929 and a third in 1934 were noted but no specific treatment was given. He returned in 1937 on the recommendation of a dentist in his home community that he have three teeth extracted. One tooth was extracted but the patient's bleeding could not be stopped in spite of transfusions, administration of neobomoplastin, epinephrine packs and so forth. On the fourth day the patient died.

Roentgenograms made in 1934 showed a destructive area in the lower portion of the left femur (fig. 88). On postmortem examination the oval area of rarefaction in the cortex of the distal third of the femur was found to be the site of a hemophilic bone cyst that had developed during the previous six years. Figure 89 shows the knee almost completely filled with old hemorrhage. The joint synovial membrane was grossly thickened and darkened and showed evidence of hemosiderin deposits in many places. There were hypertrophied synovial tags extending into the intra-articular spaces and in some places the joint cartilage was markedly thinned.

The six cases reported in the complete paper in some detail seem to be examples of the so-called hemophilic pseudotumor. These cases are similar to those previously noted in the literature. One is very similar to that reported by Firor and Woodhall. In one other case the olecranon was involved; unfortunately we have been unable to trace this patient and cannot tell what changes have developed. In four cases the lesion involved the femur and all of these patients are now dead. Three died from the effects of the pseudotumor of the thigh with subsequent fracture of the femur, erosion of the mass through the skin and terminal hemorrhage with infection. In one the patient died of hemorrhage following a tooth extraction but the changes in the roentgenogram and the findings at necropsy would indicate the beginning of a process similar to those which developed in the other cases of "pseudotumor" of the thigh.

OSTEOPOROSIS OCCURRING DURING POTASSIUM THIOCYANATE THERAPY FOR HYPERTENSIVE DISEASE*

JOHN J. HINCHEY, EDGAR A. HINES, JR. AND RALPH K. GHORMLEY

After the extensive use of potassium thiocyanate in the treatment of hypertension, occasional instances of osteoporosis and arthralgia were noted. Since no previous description of this phenomenon could be found, a further investigation was undertaken.

The records of 5,000 consecutive patients with hypertension who had been seen on two or more occasions at the Mayo Clinic in the period 1939 to 1944, inclusive, were reviewed. Potassium thiocyanate had been given to 360 patients of this group. Unexplained osteoporosis occurred in seven. Since 1944 there have been four additional patients with this syndrome. No history of trauma or injury at onset could be elicited from these patients. One or more extremities, usually the lower, were involved. Patients with involvement of the spine or pelvis were not included, as senile osteoporosis could not be excluded. Similarly omitted were those who had a diagnosis of chronic infectious arthritis, peri-arthritis, rheumatoid arthritis or fibrositis. Unexplained osteoporosis was not observed in the group of more than 5,000 patients with hypertension who were not receiving potassium thiocyanate.

CLINICAL DATA

The incidence of osteoporosis in the group of patients who were receiving potassium thiocyanate therapy was approximately 2 per cent. There were six women and five men. The age ranged from forty-six to sixty-eight years, averaging 56.5 years. The dosage of the drug varied considerably during the course of treatment, but was usually in the range of 6 to 9 grains (0.4 to 0.6 gm.) daily. Onset of symptoms associated with the osteoporosis generally occurred in three to six months after administration of the drug was started. The symptoms consisted of (1) pain on use of the extremity which began insidiously and gradually increased in severity and (2) subsequent mild swelling of the joint or joints involved, but with no acute inflammatory reaction. The severe cases simulated those of extensive post-traumatic osteoporosis. Roentgenograms, which were limited to the involved regions, revealed mild to marked diffuse osteoporosis.

Active therapeutic measures directed toward the osteoporosis were carried out in seven cases while thiocyanate therapy was being continued. These consisted of physiotherapy, active and passive movement, shoe corrections, walking-casts, elastic bandages, and preparations of calcium and phosphate for oral use. Symptoms continued to progress despite these measures in six cases. Slight improvement over a period of several months was noted in the seventh case under such measures, and the rate of improvement was accelerated when administration of the drug was stopped.

Cessation of potassium thiocyanate therapy was followed by relief in every one of the eleven cases whether or not specific measures of treatment

* Abridgment of paper published in full in the *American Journal of the Medical Sciences*, 215:514-534 (May) 1948.

were used. Improvement was generally evident in two to three months and complete in five to seven months. Administration of the drug was resumed in four instances. In two cases there was no recurrence of symptoms or of osteoporosis. Symptoms recurred in the other two but were again relieved when thiocyanate therapy was once more discontinued.

The thiocyanate levels in general varied considerably in different patients and in the same patient from time to time.

The value for blood urea was within normal limits in all cases. The blood uric acid level was normal in four cases. The sedimentation rate was elevated in two of the eleven cases, but remained so after complete recovery in both. The serum phosphate level was determined in four patients and the blood alkaline phosphatase in three. All were within the usual range of normal. The serum calcium level was determined in five instances, being within normal limits in three and slightly below normal in two. In one of these a urinary Sulkowitch test gave a grade 4 reaction (graded on the basis of 1 to 4, in which 1 represents the least, and 4 the greatest concentration of calcium).

COMMENT

No cause for this syndrome other than thiocyanate therapy could be found. Trauma at the onset was consistently denied. One patient sprained the involved ankle shortly after the initial appearance of symptoms and this sprain markedly aggravated her discomfort. No other therapeutic procedure was instituted for any significant period of time during the development of the osteoporosis in any case. Concurrent, but probably unrelated, conditions occurred in two patients. One consisted of a diarrhea beginning two months after the onset of symptoms. The other was a burn of the thumb with secondary infection. Sulfathiazole treatment was administered to the latter patient in the interval just preceding the appearance of symptoms; however, the osteoporosis in this case involved the ankles. No evidence of renal insufficiency was noted in any of these patients. The possibility of a local vascular accident with overcompensating collateral circulation and hyperemia was suggested as a cause for the osteoporosis. The absence of this syndrome in more than 5,000 consecutive patients with hypertension who did not receive potassium thiocyanate makes it extremely unlikely that a complication of the hypertensive disease was the underlying cause of the osteoporosis.

The following evidence suggests that the osteoporosis was a result of thiocyanate therapy: (1) there was a sufficient time interval between institution of the drug and onset of symptoms; (2) improvement was noted in a reasonable period of time after discontinuance of the drug, whether or not therapy was directed at the osteoporosis; (3) in six of the seven cases the usual specific therapeutic measures failed to halt progression of the osteoporosis so long as potassium thiocyanate therapy was continued; (4) increase in dosage of the drug in one instance resulted in an aggravation of symptoms within a few weeks and (5) resumption of use of the drug after recovery produced recurrence of symptoms in two of four cases, with relief after the drug was again discontinued.

A mode of action of the potassium thiocyanate must still be presumed. No marked lowering of blood pressure was noted consistently. The osteo-

porosis occurred far too infrequently to be the result of a direct action of the drug on bone itself.

Potassium thiocyanate therapy has been used in more than 100 cases of severe migraine without the production of any syndrome such as that of osteoporosis. Evidence at hand at present seems to favor a slight but prolonged interference with calcium metabolism as the mechanism of the production of the osteoporosis. The actual dosage of the drug is small, although it is in excess of those of aluminum and iron which have been recommended in different types of bone malacia. In the presence of adequate calcium intake and normal metabolism, such a slight interference with calcium metabolism would scarcely be sufficient to produce osteoporosis, and it has not occurred in the migrainous patients who represent a younger age group. However, should there be a tendency to a negative calcium balance which is so often found in individuals of the age group with which this report deals, then any additional deficiency in calcium metabolism could produce such a picture. The finding of subnormal values for serum calcium in two cases and of a grade 4 reaction to the Sulkowitch test in one case was further suggestive evidence of this mechanism. Thus all known factors, including the time element both for production of and recovery from this syndrome, the infrequency of occurrence of the syndrome, the dosage of the drug and the group of individuals dealt with, were consistent with a minor additional interference with calcium metabolism. Further investigation along these lines is being carried out at present.

Regardless of the mechanism of production of osteoporosis, one should be cognizant of the occasional occurrence of this condition and should insure adequate calcium intake in individuals who are taking potassium thiocyanate. The use of this drug in the presence of a fracture may be inadvisable, not as regards union of the fracture which is a local affair, but because any interference with calcium metabolism in the presence of an increased calcium requirement might precipitate osteoporosis. Potassium thiocyanate therapy may similarly be contraindicated in the presence of bone malacia, such as senile osteoporosis or osteitis deformans, as use of the drug could cause further increase of decalcification and aggravation of symptoms.

A Mallet Employed in the Performance of Surgical Procedures on Bone*

HENRY W. MEYERDING

A mallet which I designed in 1915 has been widely employed in the performance of operations on bone, for many years. This bone mallet has been modified so that it is more effective by giving it more weight and more strength. The advantage of the new type of mallet is that the surgeon is able to watch the cutting edge of the chisel and accurately gauge the force of the blow with a minimum of effort and without striking his hand or tearing his glove. This mallet has sufficient weight so that it can be grasped

* Accepted by the American Journal of Surgery.

close to the head and a light blow imparted to the chisel or it can be grasped further toward the end of the handle and still by wrist action the mallet strikes sufficiently hard to give any desired force. Wrist action is all that is required because of the weight of the mallet. Furthermore, this mallet is made more conical in shape so that it may be used to impart the force of the blow directly through the chisel and thus it does not tend to divert the cutting edge. In other words, it permits the surgeon to strike the head at right angles with the chisel and in the center of the head of it and at the same time to keep his eye on the cutting edge. I have often seen surgeons

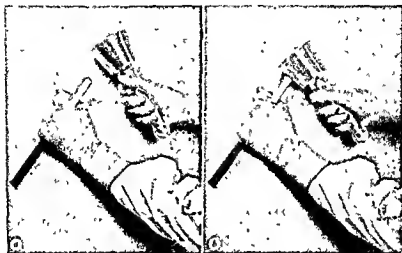


Fig 90.—Surgical mallet, *a*, before and *b*, after striking the head of the chisel.

attempting to work with too light a hammer and in striking the chisel forcefully they miss the head; a light instrument makes the operation more difficult and there is danger of sustaining injury to the hand or glove or both.

The new mallet is made of an alloy which does not tarnish and is thicker and thus stronger at the base of the head than the one described previously. It should last a surgeon for an indefinite period. It is $8\frac{3}{4}$ inches (22.2 cm.) in length, weighs 2 pounds (0.9 kg.) and has a handle that is hexagonal which facilitates grasping and holding it firmly (fig. 90).

DIAGNOSTIC CLINIC; DIFFERENTIATION BETWEEN "PSYCHOGENIC RHEUMATISM" AND TRUE RHEUMATIC DISEASE*

PHILIP S. HENCH

The most common rheumatic diseases are (1) osteo-arthritis, a nuisance but not a calamity; (2) rheumatoid arthritis, the most crippling of the chronic arthritides, and (3) primary fibrositis, a periarticular or intramuscular condition which produces aching stiffness of joints or muscles but which produces no intra-articular disease. Patients with fibrositis might be called "rheumatic," but not "arthritic."

Another common condition, "psychogenic rheumatism" (psychoneurosis affecting the musculoskeletal system), must be distinguished from the first three because, under certain circumstances, it may be mistaken for one of the other conditions.

OSTEO-ARTHRITIS

Osteo-arthritis is a composite of (1) degenerative chondritis, (2) hypertrophic and destructive (more hypertrophic than destructive) osteitis of subchondral bone, and, in addition, (3) secondary fibrositis, generally of a mild degree characterized by aching stiffness of the musculo-fibrous tissues.

This is an aging process. The cartilages degenerate; the underlying bone reacts thereto. Also the muscles and the fibrous capsule of joints lose their resiliency to a certain degree, a process called "secondary fibrositis." The latter does not produce significant muscular spasms or atrophy or flexion deformities; in these ways it differs notably from the secondary fibrositis of rheumatoid arthritis. Most important of all, the synovial membrane is not significantly affected in osteo-arthritis; it does not proliferate or produce hydrops or pannus. Hence in uncomplicated osteo-arthritis we do not see boggy hydropsical swellings, flexion deformities, and fibrous or bony ankylosis. Since, as a rule, there is no systemic disease we note no constitutional or humoral reactions: no elevation of sedimentation rates, no anemia or loss of appetite and weight. The absence of these features is important and helpful in diagnosis.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a much more widespread disease than is osteo-arthritis. Rheumatoid arthritis is a composite of (1) a proliferating synovitis, (2) an atrophic nonsuppurative epiphyseal (subchondral) osteomyelitis, (3) a destructive chondritis (from inflammation, not degeneration), (4) a subchondral osteitis which is more destructive than hypertrophic (in contrast to the "osteitis" of osteo-arthritis which is more hypertrophic than destructive), (5) a secondary periarticular and intramuscular fibrositis and (6) systemic disease. The presence of the last condition is important and helpful in differential diagnosis: the constitutional and humoral abnormalities indicative of this systemic disease are often present very early in the course of the disease. The sedimentation rate is increased in about 90 per

* Abstract of paper published in full in *Postgraduate Medicine*, 1:460-466 (June) 1947.

cent of cases; the patient usually has a hypochromic anemia with a moderate reduction in hemoglobin and erythrocyte count and some loss in weight and appetite.

The diagnosis in rheumatoid arthritis is based primarily on the objective findings (a relatively afebrile polyarthritis with early articular swellings); the constitutional reactions occur fairly early and in due time, the roentgenographic abnormalities.

CRITERIA FOR A DIAGNOSIS OF ARTHRITIS

To make a definite diagnosis of rheumatoid or of osteo-arthritis (or any other type) you must have one or two or three of the following: (1) physical signs such as the definite swellings as seen in a case of rheumatoid arthritis or the osseous nodular enlargements of Heberden's nodes in a case of osteo-arthritis; (2) constitutional reactions; (3) roentgenographic changes. As for "swellings," you must not take the patient's word; you must verify them.

NATURE OF PSYCHOGENIC RHEUMATISM

Psychogenic rheumatism is the musculoskeletal expression of functional disorders, tension states, or psychoneuroses, equivalent to the functional symptoms referred to other systems. Psychogenic rheumatism is one of the commonest causes of aches and pains in muscles, joints or both.

In most cases of psychogenic rheumatism there are only a collection of subjective symptoms without objective manifestations, but at times you actually see objective manifestations. In the Army such cases were rather numerous.

DIFFERENTIATION BETWEEN PSYCHOGENIC RHEUMATISM AND FIBROSITIS

Most of the victims of psychogenic rheumatism in civilian life do not have objective changes, merely subjective complaints. Because of the absence of objective signs and of constitutional or roentgenographic reactions, such instances of psychogenic rheumatism can be rather readily distinguished from rheumatoid or osteo-arthritis. But since the manifestations of fibrositis are also largely subjective, the distinction of psychogenic rheumatism from fibrositis is less easy and may require a rather detailed analysis of symptoms. Recently, my colleague at the Army and Navy General Hospital, Major Edward Boland, and I tabulated the chief differences between the two conditions (Tabulation).

FACTORS UNDERLYING PSYCHOGENIC RHEUMATISM

What are some of the basic difficulties which underlie the production of psychogenic rheumatism? Let me cite some of the basic difficulties present in my latest thirty civilian cases. These difficulties were derived from or concerned the following: a stern parent interfering with a child's social development; an unattractive girl dominated by her protective mother and afraid the boys were passing her by; a person who previously was "imprisoned" by her parents and who considered herself "imprisoned" by her in-laws; a veteran forced by the housing shortage to live with in-laws (enough to give anyone psychoneurosis!); a common American trouble—"one vacation in ten years"; sexual impotence of the patient or the marital

DIFFERENTIATION BETWEEN FIBROSITIS AND "PSYCHOGENIC RHEUMATISM"; GENERALITIES*

	Fibrositis, primary type	"Psychogenic rheumatism"
General attitude	Cooperative, earnest, "objective"	Tense, anxious, "subjective," defensive, antagonistic
Chief complaint	"Joints hurt and feel stiff"	"Can't quite describe it, doctor. It's like . . ."
Chief symptoms	Aching, soreness, stiffness, fatigue	Burning, tightness, weakness, numbness, tingling, queer or tired sensations
Time of day when symptoms are worse	Morning and/or late afternoon	Inconstant—often continuous day and night
Aggravation or amelioration dependent on	External or physical environment	Internal or mental environment
Effect of mental preoccupation. (theatre, movie, bridge, etc.)	No definite relief, symptoms intrude	Often marked relief but perhaps "pays for it afterwards"
Symptom Analysis		
1. Pain		
Amount	+ to ++	+ to +++
Constancy	Varies in intensity during day: worse in morning, better at noon, often worse again later in day	Tendency to be constant, "bad all the time"
Duration	Hours or days	Momentary or constant, "no different," getting worse.
Location	Remissions, exacerbations	Often not anatomical
Migration	Anatomical	Bizarre, hemalgia, etc.; may follow no anatomic pattern
2. Stiffness	May not migrate; if so migrates in anatomical fashion	Minimal or not present.
3. Fatigue	Worse after much rest (jelling). More marked in early morning. Better after mild exercise.	Jelling not characteristic.
	A.M. on waking: 0 to +	Early A.M. + to +++
	P.M. ++	May be constant
	"Disability causes fatigue"	"Fatigue causes disability"
Effect of rest	After prolonged rest—worse (jelling)	Improvement or no effect
Effect of exercise	Better, "limbers up"	Worse during and after
Effect of applied heat	Temporary relief—hours	Variable—often worse
Effect of weather	Worse when cold and damp. "Weather prophet."	Variable
Effect of therapy:		
In general	Temporary relief	"Nothing helps me, doctor"
Patient's attitude	Admits relief	Defies fudging a cure
Aspirin	Temporary relief—hours	Usually no relief (aspirin futility), or "never tried it" (aspirin intolity)
Physical therapy	Temporary relief	Variable—often worse
Response to examination	Cooperative, tenderness consistent	Fearful, resistant; "touch me not" reaction
"Extras" (associated functional complaints)	0 to +	+ to ++++
		Bizarre lumps and postures, headaches, globus hystericus, sighing respirations, precordial pains, insomnia, nervousness, tremor, etc.

* From Hensch, P. S. and Boland, E. W.: The management of chronic arthritis and other rheumatic diseases among soldiers of the United States Army. *Ann. Int. Med.* 21: 608-625 (May) 1946.

partner; June-December marriages; a spinster who had given up marriage to care for her mother whom she had thereafter unconsciously come to hate; fear of an unfaithful drunken husband; a patient whose relative had died of "rheumatism" and who feared that his own "rheumatism" might also be fatal.

Are not all these factors simply different kinds of fears and frustrations? The family physician, with his intimate knowledge of the personality and relationships of his patients, has a unique ability to spot such etiologic factors. To the extent that the general practitioner or internist or rheumatologist has a psychiatric approach he may be able to uncover the basic causes and try to help the patient to rectify them. But to discover and alleviate these causes with a large measure of success usually requires, sooner or later, the services of a psychiatrist.

"Rheumatism remedies" are of little or no avail except as they constitute mild (and generally inadequate) forms of psychotherapy. These miserable souls (and it is a matter of the soul or spirit more than of the soma) deserve something much more effective than tonsillectomy, heat and aspirin. The results of psychiatric treatment are often most gratifying. But the first move in the direction of adequate treatment is the recognition by the physician and the acceptance by the patient, that the latter has the condition, psychogenic rheumatism, which I have attempted to describe.

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CHEST

TREATMENT OF ESOPHAGEAL VARICES BY INJECTION OF A SCLEROSING SOLUTION*

HERMAN J. MOERSCH

In 1940 I reported on my initial experience with the treatment of *esophageal varices by injection of a sclerosing solution through an esophagoscope* according to the technic of Crafoord and Frenckner, and in 1941 I reported on eleven cases in which this method of treatment had been used. In the latter paper it was stated that although the results were encouraging, sufficient time had not elapsed to permit determination, with accuracy, of the efficiency of the procedure. In this paper I am reporting on my experience to date with this form of treatment.

The present study is based on ten of the eleven original cases reported in 1941, one case having been discarded because of lack of follow-up, and on twelve additional cases, a total of twenty-two cases. The patients in all cases were followed at least three years. For purposes of study, the cases were divided into three groups. The first group consisted of those cases in which the patient had undergone splenectomy for Banti's syndrome or so-called portal hypertension and in which massive gastro-intestinal bleeding was the presenting complaint. The second group consisted of cases in which the esophageal varices were secondary to hepatitis and in which no surgical interference had been attempted. The third group was made up of cases of Banti's syndrome in which treatment of esophageal varices by injection of a sclerosing solution through an esophagoscope was started first and splenectomy was performed during the course of the treatment. Massive gastro-intestinal bleeding was also the presenting complaint in all the cases in groups 2 and 3.

Sixteen of the twenty-two patients were in group 1. The first six cases were included in the report of 1941. Eleven of the sixteen patients were men and five were women. The youngest patient was eleven years old and the oldest, sixty-one. Thirteen of the sixteen patients had suffered from gastro-intestinal bleeding before splenectomy. In all sixteen cases hemorrhage since splenectomy had been copious; frequently one or more transfusions had been required. The frequency of occurrence of hemorrhages varied from once a month to once a year.

Eight of the sixteen patients in group 1 have had no further bleeding since completion of their injections. The time that has elapsed since completion of their treatment varies from three to seven years. The patients in all cases have been permitted to resume their normal activities but they have been urged to avoid sudden severe exertion and, most important of

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all, to remain at rest, should they develop an acute infection of the respiratory tract, until the infection has completely subsided. An acute infection of the respiratory tract is frequently found to be a precipitating factor in bleeding from esophageal varices; this is due to the esophagitis that may accompany such an infection. One woman in this group has undergone a normal confinement without evidence of bleeding from the esophageal varices.

Eight of the sixteen patients in group 1 had further trouble after their injections, and treatments in these cases have been classified as failures. Five of these patients died; two died of massive gastro-intestinal bleeding, one of hepatic insufficiency, one of a cerebral hemorrhage and one patient at home of an unexplained cause. Three unsuccessfully treated patients who are still living have continued to suffer from gastro-intestinal bleeding.

The second group of cases consisted of three patients. In this group, two of the patients have obtained satisfactory results from their injections and have had no further bleeding. The third patient died of a gastro-intestinal hemorrhage after having been free of bleeding for three years following the injections. Two of these cases were included in the original report in 1941.

The third group of cases comprised three patients with Banti's syndrome who were suffering from gastro-intestinal bleeding. Two of the cases were reported previously. In these cases injections into the esophageal varices were started before the spleen was removed but splenectomy was performed in the course of treatment of the varices. These were cases in which enlargement of the spleen was not apparent at the outset of treatment but was noted during the course of observation. Two of the three patients have had no further gastro-intestinal bleeding three and a half years and six and a half years, respectively, since the injections and splenectomy. The third patient has continued to have episodes of severe gastro-intestinal hemorrhage.

A review of the three groups of cases shows that satisfactory results were obtained by injection of a sclerosing solution into esophageal varices through an esophagoscope, for the control of gastro-intestinal bleeding, in twelve of the twenty-two cases. Six of the unsuccessfully treated patients have died, three of gastro-intestinal bleeding, one of hepatic insufficiency, one of cerebral hemorrhage and one of an indeterminate cause. The four remaining unsuccessfully treated patients have continued to suffer from spells of gastro-intestinal hemorrhage.

The question presents itself as to why certain patients suffering from gastro-intestinal hemorrhage from esophageal varices obtain satisfactory results from the injection of a sclerosing solution, while others do not. The age or sex of the individual was found to be of no importance in this respect. The duration of the patient's trouble and the frequency with which gastro-intestinal bleeding occurred were likewise of no importance.

It might be anticipated that the patients whose esophageal varices could not be demonstrated on roentgenologic examination would be the most suitable ones for injection therapy. This expectation, however, was not borne out by the results, for in only three of the successfully treated patients were no varices seen on roentgenologic examination of the esophagus, while in five of the unsuccessfully treated patients no varices were seen on roentgenologic examination.

It was soon noted that on roentgenologic examination of the esophagus and stomach in the cases in which gastro-intestinal bleeding continued after treatment of the esophageal varices by injection, varices occasionally were found in the cardiac end of the stomach as well as in the esophagus. In the cases in which the injections were followed by satisfactory results, varices were never demonstrable in the cardiac end of the stomach on roentgenologic examination. Realizing that esophageal varices can be overlooked on roentgenologic examination of the esophagus, it seemed more than likely that varices in the cardiac end of the stomach could also escape detection by this method of examination. Six of the ten unsuccessfully treated patients were found, on gastroscopic examination, to have gastric varices. In two of these six cases roentgenoscopic examination of the stomach had failed to reveal the varices; in both of these cases the diagnosis of gastric varices was confirmed at necropsy. Only one of the successfully treated patients in this study was submitted to gastroscopic examination; this examination failed to reveal varices in the cardia. It is now a routine for me to perform a gastroscopic examination on every patient in whom the treatment of varices of the esophagus by injection is contemplated. So far the procedure has been employed without untoward incident.

That bleeding occurs from gastric varices and that the sclerosing of esophageal varices in a case of this type is of little value are well borne out in two cases in group 1. One patient had suffered repeatedly from severe gastro-intestinal hemorrhage. Although roentgenologic examination of the esophagus failed to demonstrate esophageal varices, esophagoscopy showed them to be present up to the middle third of the esophagus. In spite of repeated satisfactory injections the patient continued to have gastro-intestinal bleeding. Suspecting the presence of gastric varices, I performed gastroscopy and found varices in the cardiac end of the stomach. It seemed obvious that further injections would be of doubtful value. Some weeks later the patient lost copious amounts of blood by bowel and it was impossible to control the bleeding. On esophagoscopy no bleeding point could be found in the esophagus, but when the esophagoscope was introduced into the stomach approximately a pint of blood was regurgitated through the instrument. In spite of all restorative measures that could be employed, the patient continued to bleed and died several days later. At necropsy varices were demonstrated in the esophagus and the cardiac end of the stomach, and the bleeding point from which the fatal hemorrhage occurred was identified as gastric in origin (fig. 91).

Another patient also suffered from a gastro-intestinal hemorrhage which resulted in death; at necropsy the bleeding point was found to be a gastric varix (fig. 92). It is readily apparent that the presence of varices in the cardiac end of the stomach is a contraindication to the injection type of treatment of esophageal varices.

It is interesting to speculate as to what occurs in the esophageal varices after injection of a sclerosing solution. Sanison and Force reported that in a case in which treatment of esophageal varices by injection of a sclerosing solution through an esophagoscope had been carried out, the veins were found at necropsy to be well sclerosed. Trolle and Trolle, however, were unable to demonstrate such changes in one case of esophageal varices in which monoethanolamineoleate (varcx) was used as the sclerosing agent.



Fig. 91.—Lower end of esophagus and cardiac end of stomach in case 15.

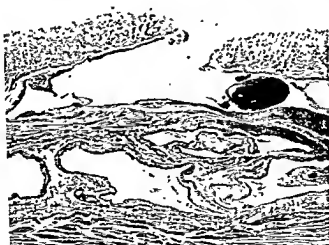


Fig. 92.—Section through bleeding point in gastric mucosa showing opening of vessel into gastric lumen (X13).

On esophagoscopic examination following satisfactory injection of a sclerosing solution of sodium morrhuate into esophageal varices, a diminution in the size of the varices will be found to have occurred. This finding

has been corroborated by Crafoord and Frenckner, Samson and Foree, and Patterson and Rouse. In this study, in two of the cases in which death occurred and in which postmortem studies were available, the vessels in the wall of the esophagus were found not to be obliterated. A definite perivenous fibrosis with thickening of the intima was noted (fig. 92). Such changes would naturally aid in making the varices less subject to perforation, with resultant bleeding.

In suitably selected cases of esophageal varices in which there is no extension of the varices into the cardiac end of the stomach, satisfactory results may be expected from injection of a sclerosing solution into the varices through the esophagoscope. In cases in which the varices involve the cardiac end of the stomach as well as the esophagus, other methods of treatment are indicated. Two methods of treatment in this latter type of case are especially worthy of consideration. The first is the establishment of a portal caval anastomosis according to the technic described by Blake-more; the other is resection of the lower end of the esophagus and the cardiac end of the stomach as reported by Phemister. One of the patients in this study was operated on by Phemister by this method with very satisfactory results. Both of these procedures are deserving of careful consideration, but time must pass before it can be determined how much they may ameliorate the course of the disease.

SUMMARY AND CONCLUSIONS

The results of treatment in twenty-two cases of esophageal varices in which gastro-intestinal hemorrhages occurred are reported; in these cases the patients were treated by the injection of a sclerosing solution into the varices through the esophagoscope. Twelve of the patients have had no further bleeding after treatment. All twelve have gone longer than three years without bleeding, and eight have gone more than four years without bleeding.

Patients in whom satisfactory results were not obtained by injection of a sclerosing solution invariably were found to have varices in the cardiac end of the stomach as well as in the esophagus, which was not true in the successfully treated cases.

Roentgenologic examination is of great value in the diagnosis of esophageal varices but is not infallible. In doubtful cases esophagoscopy should be employed.

In cases of varices in which the cardiac end of the stomach as well as the esophagus is involved, some form of treatment other than that of injection of a sclerosing solution, such as portal caval anastomosis or resection of the cardiac end of the stomach and lower end of the esophagus, should be considered; such an alternate form of treatment eventually may even become the procedure of choice in uncomplicated cases of esophageal varices.

RECOGNITION AND MANAGEMENT OF ESOPHAGEAL DISEASES*

HERBERT W. SCHMIDT

Clinical interest in esophageal disease is relatively recent. This is due to the fact that in the past there was no adequate treatment for many of these conditions. Since the recent marked improvement in thoracic surgical technic, however, it has been possible to institute curative treatment for many lesions of the esophagus, and to carry out such therapy with a relatively low mortality rate. This has led to increased knowledge and interest in esophageal disease.

ANATOMIC ASPECTS

The esophagus is a tubular organ, the proximal portion of which is continuous with the distal portion of the pharynx. It arises posterior to the cricoid cartilage and anterior to the sixth cervical vertebra, and extends inferiorly in the posterior mediastinum through the diaphragmatic esophageal hiatus into the abdominal cavity. The inferior portion of the esophagus ends at the superior aspect of the stomach, which normally is situated between the tenth and the twelfth thoracic vertebrae. The mucous membrane of the esophagus is stratified squamous epithelium, and adjacent to this there is a tough, thick, submucosal layer. The muscular coats are composed of an inner circular layer and an outer longitudinal layer. The former predominates in the distal portion and the latter predominates in the proximal fourth portion of the organ. The type of muscle varies with various species. In man, the proximal third part of the esophagus is composed of striated muscle, the middle third part is formed of both striated and smooth muscle, and the distal third part is composed of smooth muscle. The diameter of the lumen of the esophagus, in general, increases from the proximal portion distally. The narrowest portion is the esophageal introitus. Narrowing of the lumen is found at the level of the aortic arch, the left main bronchus, and the diaphragm. The nerve supply arises from the vagus and sympathetic systems.

PHYSIOLOGIC ASPECTS

This important organ has only one function: that of conveying food from the pharynx to the stomach. The act of swallowing occurs in three stages. It is beyond the scope of this paper to go into the details of this.

The vagus and sympathetic nerves innervate the esophagus. It is rather generally agreed that the vagus nervous system supplies most of the afferent and efferent impulses for the organ. The role of the sympathetic nervous system in supplying the esophagus is not well known.

DIAGNOSIS IN GENERAL

Esophageal pain may occur secondary to esophageal spasm, esophageal distention or ulceration. The painful sensations usually are felt in the retrosternal or retroxiphoid regions, but may be referred over the anterior part of the thorax and into the neck, or into the external auditory canals

* From the Medical Annals of the District of Columbia, 17:81-91; 132-133 (Feb.) 1948.

and into the angles of the jaws. The pain may be referred to the back at the level of the tenth and twelfth thoracic vertebrae, or it may be referred down both arms. Thus, it has been confused with the pain caused by coronary disease or disease of the gallbladder.

In the evaluation of any instance of esophageal disease, it is well to obtain the history of the patient in detail. The patient who has rapid, progressive dysphagia of only a few months' duration generally has a cancer of the esophagus. The patient who has more difficulty in swallowing liquids than in swallowing solids and in whom the liquids regurgitate out through the nose as a rule will have a neurologic condition, and no lesion will be disclosed in the esophagus during esophagoscopy. Accidents involving foreign bodies are accompanied by sudden severe dysphagia after an episode of choking.

In a consideration of the functional and organic conditions which most frequently affect the esophagus, it might be well to give some attention to those conditions which can cause difficulty in the proximal portion,

TABULATION

MOST COMMON CONDITIONS WHICH CAUSE DYSPHAGIA IN SUPERIOR PORTION OF ESOPHAGUS AT CRICOPHARYNGEAL LEVEL

- 1 Intrinsic lesions of the esophagus
 - a Carcinoma
 - b Benign stricture
 - c Pharyngo-esophageal diverticulum with secondary esophageal stenosis
- 2 Neurologic lesions
 - a Bulbar palsy
 - b Atrophic lateral sclerosis with bulbar involvement
 - c Infantile paralysis with bulbar involvement
 - d Myasthenia gravis
- 3 Extrinsic lesions
 - a Laryngeal lesions
 - (1) Inflammatory
 - (2) Neoplastic
 - b Tumors of the neck
 - (1) Gutter
 - (2) Other tumors
- 4 Foreign bodies
- 5 Functional conditions
 - a Functional dysphagia
 - b Hysterical dysphagia

and then to discuss those conditions which are found in the more distal portions of the organ. It is obvious that some of the conditions, such as stricture and tumor, can affect any part of the esophagus.

The most common conditions which cause dysphagia in the superior portion of the esophagus at the cricopharyngeal level are listed in the tabulation.

PHARYNGO-ESOPHAGEAL DIVERTICULUM

This is really a false diverticulum of the pharynx, but it is well to consider it with esophageal lesions because of its close proximity to the esophagus and because, as the lesion becomes larger, it will cause pressure on the superior portion of the esophagus to such a degree that complete esophageal obstruction may occur. The lesion is really a hernia in which

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the mucosal elements of the pharynx herniate through the muscular elements. It is possible that it is the result of rapid swallowing and the increased force necessary to overcome the tone of the cricopharyngeus sphincter.

This lesion usually occurs after a person is forty years of age. It is eight times as frequent in men as in women. Symptoms may vary. At first there may be a tickling sensation in the pharynx. In the past, this at times was attributed to "too prominent a uvula," and we have seen patients who have undergone uvulectomy in an erroneous attempt to correct the early symptoms of a pharyngeal diverticulum. As the size of the pharyngeal sac increases, particles of food will become lodged in it



Fig. 93.—Pharyngeal diverticulum causing extrinsic pressure on the superior portion of the esophagus.

and remain incarcerated for variable periods. The most frequent offender is meat. As the sac becomes larger, a gurgle almost always is heard after the act of swallowing. The patient frequently will refuse to dine with friends because of this sound. As the sac enlarges, it may descend into the thorax and cause secondary esophageal obstruction (fig. 93). A cough frequently develops which usually is most troublesome at night because of the overflow of fluid and food from the sac into the respiratory passages. Thus, aspirational tracheobronchitis, pneumonia or pulmonary abscess may develop secondary to this lesion.

The physical observations are typical in about 90 per cent of cases of pharyngeal diverticulum. They are obtained by having the patient flex his head slightly and swallow water. After the patient has swallowed,

pressure is exerted externally on the neck and a gurgle is heard. Since most of the diverticula arise from the left and posterior wall of the pharynx, pressure is exerted over the caudal third portion of the left sternocleidomastoid muscle. The diagnosis is made by roentgenologic examination of the pharynx after the patient has swallowed barium sulfate. The barium enters the herniated portion of the pharynx and appears as a globular mass. The outstanding feature of esophagoscopy is the ease with which it is possible to enter the pharyngeal sac. The situation of the orifice of the sac as a rule is posterior, to either the left or right.

The treatment of choice is surgical excision performed in one stage.

DIVERTICULUM OF THE LOWER PART OF THE ESOPHAGUS

Diverticula of the middle third part of the esophagus are thought to be caused by traction on a portion of the esophageal wall exerted by

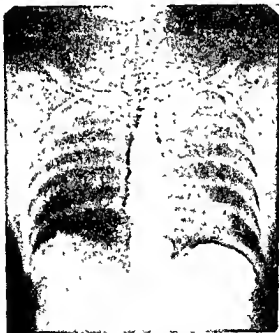


Fig. 94.—Asymptomatic diverticulum of the middle third part of the esophagus which was found accidentally while the stomach was being examined for a possible lesion. Note the esophageal hiatal hernia which was causing the patient's symptoms.

inflamed mediastinal lymph nodes. It is important to know that such diverticula rarely cause symptoms. About the only symptom they might produce is secondary spasm of the distal half of the esophagus. On extremely rare occasions they have been reported as having eroded into the left bronchial tree and caused an esophagobronchial fistula. The most important feature to be remembered about uncomplicated diverticula which occur at this level is that they rarely require any form of treatment (fig. 94).

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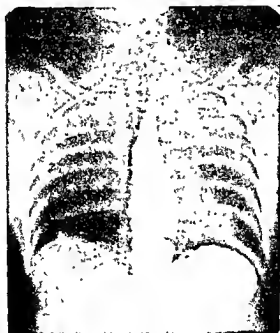


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Epiphrenic diverticula occur just proximal to the cardia, and may reach a large size. Material from a large sac may be regurgitated into the mouth and cause nocturnal cough as a result of aspiration. It is of interest to find a large diverticulum just proximal to a sphincter. The occurrence of such a lesion in this situation may be due to the force exerted in this region which is necessary to overcome the cardiac sphincter (fig. 95).



Fig 95—Large esophageal diverticulum situated just proximal to the cardia.

The diagnosis is made by roentgenologic means.

The treatment of the larger epiphrenic diverticula which cause sufficient symptoms is surgical excision.

ESOPHAGEAL VARICES

The causative background of the formation of esophageal varices is unknown. Various theories have been presented. Some workers feel that the primary disturbance lies in the vascular regulatory mechanism of the spleen. They believe that arterial blood flows with very little obstruction into the venous system and produces a state similar to an arteriovenous fistula. Other men think that the difficulties arise from obstruction in the splenic or portal vein, which in turn causes increased pressure in the portal or splenic venous system. Esophageal varices result. The veins which lie in the submucosa of the esophagus are poorly supported by connective tissue. They lie very close to the mucosal surface, and thus dilate very rapidly when an increased amount of blood flows through them.

When seen roentgenoscopically, esophageal varices appear as elongated folds running parallel to the longitudinal axis of the esophagus. At times it is impossible to demonstrate esophageal varices by roentgenologic means. When seen at esophagoscopy, the veins have the appearance of bluish red folds which course in the longitudinal axis of the esophagus. It is easy to compress them with the tip of the esophagoscope. They increase in size when the patient strains.

Various procedures have been recommended for the prevention of bleeding from esophageal varices. Splenectomy has been performed in an attempt to reduce the volume of blood flowing through the portal system in cases in which the varices have been caused by splenic anemia. Hemorrhage after splenectomy occurs in about 50 per cent of cases, and fatal bleeding is a frequent cause of death.

Crafoord and Freuckner, and Moersch have injected esophageal varices with sclerosing solutions through an esophagoscope. It is extremely important to limit this type of treatment to those patients who do not exhibit signs of gastric varices at the time of gastroscopy, since it is impossible to treat gastric varices through the esophagoscope.

More recently, venous anastomoses have been established between the portal and systemic circulations. The left renal and splenic veins have been anastomosed. It is too early to evaluate adequately the merits of these procedures.

ESOPHAGITIS

Esophagitis is the most frequent lesion of the esophagus. It may occur after prolonged vomiting, the passage of stomach tubes or the ingestion of irritants. It may occur secondary to esophageal hiatal hernia of the sliding type, since in such a condition the cardia loses much of its sphincteric value and gastric contents will be regurgitated back into the esophagus. The hydrochloric acid of the stomach may prove very irritating to the esophageal mucous membrane, and may even cause ulceration and formation of stricture. Esophagitis may occur with any acute systemic infection. The symptoms of esophagitis as a rule are a sensation of burning in the retrosternal region, dysphagia and painful swallowing.

If the esophagitis is severe, it may be necessary to withhold feedings for a few days and to give food and fluids parenterally. At times it is necessary to administer morphine for the relief of pain. After the acute manifestations subside, the patient can begin to employ a liquid diet and then a bland diet. If the esophagitis has been severe, the condition of the patient should be followed very carefully for at least six to eight weeks to make certain that an esophageal stricture does not develop. At times it takes this long a period before the connective-tissue reaction of the esophagus becomes manifest and causes a stricture.

STRICTURES OF THE ESOPHAGUS

As severe esophagitis heals, it may lead to the formation of a stricture (fig. 96). Concentrated alkalis, such as lye, and strong acids, taken with suicidal intent or by accident, can very readily cause severe ulcerative esophagitis which, while healing, will cause a connective-tissue reaction with formation of scar tissue sufficient to cause a stricture. The pernicious vomiting of pregnancy or the chronic regurgitation of gastric acids, such

as occurs with esophageal hiatal hernia, also can cause esophageal stricture. If the development of a stricture is feared, it is well to ask the patient to swallow a silk thread and keep this thread in place during the period of observation. Then, if the esophagus should suddenly completely close as a result of a stricture, with the thread in place it will be possible to open the esophagus by means of dilation. The thread serves as a guide for dilating instruments. If the esophagus closes completely without a thread in place, the problem becomes a much more serious one. The patient should swallow at least 15 feet (4.6 m.) of twisted silk thread. This enables the distal end of the thread to become engaged in the loops of small bowel, and thus makes it possible to use it as a guide in the passing of the dilating sounds.



Fig. 96a.—Stricture of the esophagus which followed typhoid fever; a foreign body is lodged in the stricture. At the time of roentgenologic examination of the esophagus this was thought to be due to tumor. b. Esophagoscopy revealed a plum pit, which was removed. c. The esophagus after removal of the foreign body and esophageal dilation.

Esophageal strictures are, for the most part, best treated by dilating them with graduated sounds. If the injured portion of esophagus can be used again as a tube to convey food, it will be far more satisfactory than the construction of an artificial esophagus or the performance of resection of the involved part of the esophagus and establishment of an esophago-gastric anastomosis. In rare instances, such procedures are necessary, but the end results of dilation of esophageal strictures generally are excellent.

FOREIGN BODIES

Accidents involving the esophagus caused by the lodging of foreign bodies usually occur as the result of carelessness (fig. 97). Most of them occur in young children who have placed undigestible objects in the mouth and have accidentally swallowed them. An open safety pin carelessly left in the baby's crib is a foreign body which the esophagoscopist

frequently sees lodged in the gullet. Carelessness in the preparation of food will account for some of the accidents. Pieces of wire, broken glass and staples have been swallowed with food. Adults who wear upper dentures may accidentally swallow undigestible material such as chicken bones, since during the act of chewing they cannot feel these objects against the hard and soft palate because of the presence of the denture.

The first symptom of ingestion of a foreign body is a choking or strangling sensation at the cricopharyngeal level. Most foreign bodies become lodged at this level. After they become impinged, it generally becomes impossible for the victim to swallow, because of pain. If the foreign body is opaque in the roentgenogram, it will be possible to determine its size



Fig. 27.—Rolled-up sulfathiazole ointment tube swallowed accidentally by an infant.

and location. The widest diameter of the foreign body presents itself in the coronal plane, since the diameter of the esophagus is greatest in this plane. Nonopaque foreign bodies will not be seen roentgenologically. If the history is strongly suggestive of the presence of an esophageal foreign body, esophagoscopy removal of the foreign body should be accomplished with the least possible delay.

CARCINOMA OF THE ESOPHAGUS

The esophagus is the site of carcinoma in about 6 per cent of all cases of carcinoma. Carcinoma of the esophagus occurs in men five times as frequently as it occurs in women. In women carcinoma frequently is found at the cricopharyngeal level, whereas in men it is frequently found at the esophagogastric junction. The history includes rapidly developing,

progressive dysphagia so far as solids are concerned; then dysphagia in respect to soft foods, and finally, in respect to liquids. Rarely, hemorrhage or pain will be the first symptom. As the esophageal obstruction progresses, regurgitation, with the aspiration of esophageal contents, will be noticed. There will be a rapid loss of weight and strength as a result of inadequate caloric intake.

The diagnosis is made by roentgenologic and esophagoscopy study of the lesion. Roentgenograms made with the aid of barium disclose an irregular filling defect. To make absolutely certain of the diagnosis, it is necessary that esophagoscopy be carried out and that tissue be removed for microscopic examination. At times, carcinoma at the esophagogastric junction will cause a foreshortening of the esophagus and will cause the stomach to be drawn into the thorax. To the roentgenologist, the lesion will look like a short-esophagus type of hiatal hernia. Biopsy will be necessary to establish a diagnosis. Conversely, in the roentgenogram foreign bodies in the esophagus at times will resemble a carcinoma.

The only curative treatment for carcinoma of the esophagus is resection of the lesion, when this can be accomplished. Unfortunately, metastasis occurs relatively early in many patients, and resection then has only a palliative effect.

Palliative procedures that can be employed are (1) deep roentgen-ray therapy, (2) esophageal dilation, and (3) gastrostomy. At the clinic it has been our policy to try to keep the esophageal lumen open as long as possible in order that the patient may eat. We have tried to avoid gastrostomy whenever possible.

Other malignant tumors of the esophagus are rhabdomyosarcoma, which arises from the striated-muscle portion of the esophagus, and leiomyosarcoma, which arises from the smooth-muscle portion of the esophagus. These are very rare.

BENIGN TUMORS

Benign tumors of the esophagus are relatively rare. They may become large before they cause symptoms. Fifteen instances of benign tumor of the esophagus were found in a group of 11,000 patients who came to the Mayo Clinic because of dysphagia. On the other hand, forty-four instances of benign tumor were found during 7,459 postmortem examinations.

Leiomyomas are the most common benign tumors of the esophagus. Other benign tumors are hemangiomas, papillomas, polyps, neurofibromas, lipomas, adenomas, myofibromas and cysts.

For the purpose of description, tumors have been classified as (1) mucosal or intra-esophageal, or (2) intramural or extramucosal tumors, depending on where they arise in the wall of the esophagus. Those which present on the mucosal surface are very likely to become polypoid; a long pedicle may develop as a result of the constant pull exerted by the peristaltic action of the esophagus. Pedunculated tumors may be regurgitated into the mouth; at times they will protrude from the mouth after vomiting. They may cause laryngeal obstruction in this position. Tumors arising from the outer coats of the esophagus seldom become pedunculated.

When benign tumors of the esophagus produce symptoms, the symptoms usually are those of dysphagia, or, the tumor may be regurgitated into

the mouth. Rarely will the mucous membrane become ulcerative and cause hemorrhage. Tumors in the lower part of the esophagus may cause epigastric distress. Benign tumors cause a smooth filling defect in roentgenograms of the esophagus. At times, when they become large, they may cause such a degree of dilation of the esophagus that the picture may resemble that of cardiospasm. Esophagoscopy may reveal a pedunculated tumor, but when the tumor arises in the wall of the esophagus it may be impossible to distinguish the picture of benign tumor from that seen when extrinsic pressure on the esophagus exists.

It is impossible at times to secure a satisfactory specimen for biopsy from a benign tumor.

A small, asymptomatic benign tumor will not require treatment. Those tumors that produce symptoms should be removed surgically.

Cysts may occur in the esophageal wall and cause variable degrees of esophageal obstruction. They should be removed when they are causing symptoms or when the diagnosis remains in doubt.

DIFFUSE SPASM OF THE ESOPHAGUS

Spasm of the distal portion of the esophagus can be produced experimentally by the stimulation of various nerves. Clinically, spasm of the lower part of the esophagus has been observed in diseases of the esophagus, stomach, gallbladder and biliary tract. Occasionally, it has been observed in cases of severe organic heart disease. Diffuse spasm of the distal half of the esophagus may occur in highly nervous persons when they are subjected to undue emotional stress and strain.

The chief characteristics of diffuse spasm of the distal half of the esophagus are dysphagia and pain. The pain is characterized by severe retro-xiphoid or retrosternal pain which will extend over the superior part of the anterior thorax and into the arms and the mandible. At times it will extend to the external auditory canal. It may extend through to the lower thoracic part of the spinal column and thus may be confused with disease of the gallbladder. The pain at times will be thought to be caused by organic heart disease or by various lesions in the stomach.

Roentgenologic examination of the esophagus is very important. If a patient is free of symptoms at any particular time, the results of roentgenologic studies may be negative. If the study is made during a period when the patient is having symptoms, three main pictures may be seen: (1) diffuse irregular spasm, (2) multiple spastic segments (fig. 98) and (3) diffuse narrowing of the distal half of the esophagus. The picture should not be confused with that of cardiospasm, in which the obstruction exists only at the cardia and in which one sees marked dilation of the esophagus above the level of the obstruction.

Esophagoscopy examination will reveal diffuse spasm of the distal half of the esophagus, and the examination may be difficult because of this spasm. Spasm may exist even though the procedure be performed with the patient under the influence of general anesthesia.

No satisfactory treatment for diffuse spasm of the distal half of the esophagus has as yet been evolved. It is extremely important that such factors as fatigue, anxiety, nervous strain and emotional upsets be avoided, because these almost always precipitate exacerbation of symptoms. Al-

most all persons who suffer from primary diffuse spasm of the lower part of the esophagus are tense and nervous. At times esophagoscopy and dilation of the esophagus by means of esophageal sounds have given some relief, but the results are very poor in comparison with those obtained by dilation of the esophagus in cases of cardiospasm.



Fig. 98.—Multiple spastic segments of the distal half of the esophagus

CARDIOSPASM

Cardiospasm is an occlusion at the cardiac sphincter without an organic lesion at the site of obstruction. There is dilation of the esophagus above the site of obstruction. Clinically, there usually is marked dysphagia at the retroxiphoid level, with regurgitation. Another symptom may be retroxiphoid pain, which may or may not extend to the lower thoracic part of the spinal column or over the anterior part of the thorax to the external auditory canals and the mandible. At times this pain will extend to the shoulders and down the arms. Nocturnal regurgitation of esophageal contents may occur, with aspiration of part of this material into the tracheobronchial tree. Thus, aspirational tracheobronchitis, pneumonitis (fig. 99) or abscess of the lung may occur. The right lung is affected more frequently than the left one.

The cause of cardiospasm is not known, but the condition probably is due to some pathologic process in the nerve plexuses of Meissner and Auerbach. Some workers have proposed the theory that cardiospasm is

a functional condition secondary to emotional and nerve strain. This is very hard to accept, since instances of cardiospasm occurring in the newborn have been reported. Also, as a group, patients who have this lesion are not neurotic.

Cardiospasm occurs more frequently in men than in women: the ratio in this respect is 3:2. It may occur at any age. Marked dehydration and loss of weight may occur. Death may ensue if treatment is not carried out when cardiospasm is severe.

The type of dysphagia from which patients with cardiospasm suffer is of interest. They are rather likely to experience most of their difficulties in the ingestion of cold liquids or foods, apples, popcorn, or carbonated beverages. Solid foods may be swallowed with greater ease than liquids. Complete esophageal obstruction may develop in the patient who has cardiospasm. The esophagus may hold as much as 2 to 3 liters. Some



Fig 99a and b—Cardiospasm with aspirational pneumonia

patients will learn various methods of increasing intra-esophageal pressure so that food will be forced into the stomach. This, however, may involve some danger, since esophageal perforation might be caused thereby.

The diagnosis of cardiospasm can be made by the history, roentgenologic study of the esophagus and esophagoscopy. Roentgenologic study of the esophagus with barium sulfate will reveal a smooth, regular obstruction at the cardia, with a widely dilated esophagus which will become fusiform, flask-shaped or rather tortuous in its caudal portion, resembling a plumber's U-shaped drain trap.

The treatment of choice in the great majority of cases of cardiospasm is esophageal dilation by means of the Plummer dilator. This procedure gives very satisfactory results and is accompanied by very little hazard when it is used correctly. The patient is asked to swallow 15 feet (4.6 m.) of twisted silk thread at the rate of 1 foot (0.3 m.) an hour. This will be enough thread, if it is swallowed correctly, to engage the distal end in the loops of jejunum. The thread is passed through the cannulated portion

of the dilating instrument and is used as a guide. The first treatment for cardiospasm consists of passage of a no. 50 French sound past the cardia. Two days later the Plummer hydrostatic dilator is used. The distance from the upper teeth to the cardia is measured by, first, the passage of a blunt no. 41 French sound. The hydrostatic dilator is passed so its central portion is securely engaged in the cardia, and the dilator is distended up to its full capacity at a pressure of 22 to 24 feet (6.7 to 7.3 m.) of water.

The results of dilation are very satisfactory. Before the patient is dismissed, it is ascertained that he is able to eat all types of food. If there is dysphagia in respect to any food, further dilation may be necessary. If a patient is completely relieved by dilation, the chances are very good that he will never require further treatment. A certain number of patients may experience recurrence of symptoms shortly, or as long as seventeen years, after treatment.

When the esophagus is large and tortuous, it is at times impossible to dilate it. In such a case it may be necessary to carry out esophago-gastrostomy.

TRAUMATIC PERFORATION OF THE ESOPHAGUS

The esophagus may be perforated by instrumentation, by penetrating or perforating wounds to the thorax, or by the accidental ingestion of foreign bodies. At times perforation occurs secondary to severe esophagitis or to a neoplasm. Rarely, the esophagus will be perforated by a direct blow to the thorax or by forcible attempts to swallow or by vomiting.

The first symptom of perforation usually is pain in the retrosternal or cervical region. If the perforation is situated low in the esophagus, there may be reflex pain and rigidity over the abdomen, and the physician will suspect that an abdominal viscus has been ruptured.

The first signs of esophageal perforation as a rule are those of fever and cervical subcutaneous emphysema. As time goes on, signs of mediastinal widening or fluid in the left pleural space will develop.

Esophageal perforation is always serious because of the mediastinitis that develops. As soon as the diagnosis has been made, the mediastinum should be drained. In perforation of the upper part of the esophagus, this drainage can be established in the cervical region. In perforations around the cardia, transthoracic extrapleural mediastinotomy will have to be carried out for this purpose.

In war wounds of the thorax, when esophageal perforation was suspected, early drainage was the rule in most instances. The results of early drainage are far superior to those obtained when expectant treatment with chemotherapeutic compounds is relied upon.

ESOPHAGEAL HIATAL HERNIA

Esophageal hiatal hernia is the most frequent type of diaphragmatic hernia. There are three types of hiatal hernia: (1) the sliding type, (2) the short-esophagus type, and (3) the para-esophageal type.

In the sliding type of hernia, the stomach slides up into the thorax through the esophageal hiatus in the region of the posterior mediastinum. The portion of the stomach that has protruded above the diaphragm will increase during recumbency or when pressure is applied to the anterior

abdominal wall. In small hernias of this type, the stomach will descend to its normal position when the patient stands up. The hernia can then be demonstrated only during recumbency or by the exertion of pressure on the anterior abdominal wall. This is the most common type of hiatal hernia.

The short-esophagus type of hiatal hernia is the second most common type of hiatal hernia. The esophagus is foreshortened by a previous inflammatory process or by a congenital anomaly. Most of these lesions, when seen in adult persons, are acquired (fig 100).

The para-esophageal type of hiatal hernia is the least common of the three types of hiatal hernia. The esophagogastric junction may occupy



Fig. 100—Short esophagus type of esophageal hiatal hernia, the first symptoms of which developed when the patient was fifty years old

its normal level, but a portion of the fundus of the stomach will project up into the thorax through the esophageal hiatus, and will cause extrinsic pressure on the lowermost part of the left lateral wall of the esophagus.

The most frequent symptoms of hiatal hernia are the regurgitation of sour-tasting gastric secretion, pain, dysphagia and hemorrhage. The regurgitation of gastric content occurs during recumbency, when the patient is bending over, or when external pressure is applied to the abdominal wall. It occurs as a result of the fact that the cardia loses most, if not all, of its sphincteric action when sliding and short-esophagus hernias of any size occur. Gastric contents will enter the esophagus during recumbency or when pressure is placed on the anterior wall of the abdomen.

This may lead to esophagitis or even ulceration, with a dull retrosternal burning. At times the symptoms may simulate those of peptic ulcer, except for the fact that food aggravates the distress.

Esophageal hiatal hernia may cause a reflex diffuse spasm of the lower part of the esophagus, and with it, esophageal pain and dysphagia. The symptoms may be thought to be caused by heart disease, disease of the gallbladder, peptic ulcer or cardiospasm.

At times large hiatal hernias are asymptomatic, or the patient will come to the physician because of the symptoms of secondary anemia resulting from an oozing type of bleeding which may occur in the stomach or at the esophagogastric junction, brought about by mechanical or chemical trauma. At times large hernias may become strangulated; this will cause severe pain and dysphagia.

Roentgenologic studies of the esophagus and stomach with the patient in the recumbent position and with pressure being exerted on the anterior wall of the abdomen almost always will demonstrate the hiatal hernia. Esophagoscopy should be carried out for all patients who exhibit the roentgenologic picture of hiatal hernia, to exclude the possible presence of such a lesion as carcinoma of the lower part of the esophagus, with foreshortening of the esophagus. A carcinoma of the esophagus will cause the superior portion of the stomach to herniate through the esophageal hiatus, and make it appear that a short-esophagus type of lesion is present.

The chief observation at the time of esophagoscopy in the sliding type of hernia is that the cardia has lost most of its sphincteric action; the physician will see gastric juice coming up into the esophagus. The lower part of the esophagus at times will show signs of esophagitis. A variable portion of the stomach will be situated above the diaphragmatic level.

The short-esophagus type of hernia generally will, at esophagoscopy, reveal the esophagogastric junction to be markedly inflamed and almost always ulcerated. At times this ulceration is severe, and it is impossible to distinguish between this lesion and a carcinoma without biopsy. When there is any doubt, a specimen for biopsy always should be taken. As a rule, the cardia is gaping, and gastric juice can be seen being regurgitated up into the esophagus.

In the presence of a para-esophageal hiatal hernia, variable degrees of extrinsic pressure will be exerted on the left lateral wall of the lower part of the esophagus.

Most patients who have esophageal hiatal hernias are obese. It is urgent that they reduce weight and avoid pressure on the anterior wall of the abdomen as much as possible. Belts and corsets should be discarded. If there is ulceration at the esophagogastric junction, a diet such as is prescribed for an ambulatory patient with ulcer, with some form of antacid, should be used. The symptoms caused by small sliding and para-esophageal hiatal hernias usually will be corrected by the afore-mentioned conservative methods. When symptoms persist and when the hernia is large, surgical repair will be necessary.

SURGICAL MANAGEMENT OF ACQUIRED STRICTURE OF THE ESOPHAGUS WITH ESOPHAGOBRONCHIAL FISTULA AND BRONCHIECTASIS OF ENTIRE RIGHT LUNG: REPORT OF CASE*

O. THERON CLAGETT AND HERBERT W. SCHMIDT

Bronchiectasis involving an entire lung does not occur frequently although it is not a rare condition. Strictures of the esophagus occurring as a result of ingestion of lye are, unfortunately, rather common. Acquired fistulas between the esophagus and the major bronchi or trachea are unusual. The occurrence of all three of these conditions in the same patient is certainly remarkable and presents formidable problems in regard to management. A report of such a case in which surgical management was successful appears warranted.

REPORT OF CASE

A white man, twenty-five years of age, registered at the Mayo Clinic on August 24, 1946. At two years of age he had accidentally swallowed lye and a stricture of the esophagus had developed. This had been treated with repeated esophageal dilatations and the patient had been able to take a fairly normal diet. At the age of twelve years he had pneumonia. The periodic esophageal dilatations were not performed during this illness and the esophagus became completely closed. Gastrostomy had been performed and all food and liquid had been given by this route for the thirteen years previous to admission to the clinic. Since the age of two years, when the patient swallowed lye, he had been troubled with a mild, chronic cough productive of some mucopurulent material. After the pneumonia at the age of twelve years the cough became much worse. Three to four ounces (90 to 120 c.c.) of thick, purulent, blood-streaked sputum was raised daily. The patient had never been able to work. Clubbing of the fingers had developed after the pneumonia. Recently there had been rather severe hemoptysis. The patient had noted that if the feedings given through the gastric stoma were too thin or if they were too large he would cough up some of the food that had been administered. A diagnosis of bronchiectasis of the right lung and of a fistula between the right bronchus and esophagus had been made elsewhere.

On physical examination the patient was observed to be a tall, very thin, white man, weighing only 110 pounds (49.9 kg.). There was no expansion of the right side of the chest and the interspaces were narrowed. The right side of the chest was dull to percussion. Numerous coarse rales were heard on auscultation. There was marked clubbing of the fingers and toes. A gastric stoma, with tube in place, was noted in the left upper part of the abdomen. Physical examination was not remarkable otherwise.

The concentration of the hemoglobin was 14.2 gm. per 100 c.c. of blood. The leukocyte count was 14,600 per cubic millimeter of blood with a normal distribution. The sedimentation rate was 32 mm. in one hour (Westergren method). Examinations of sputum for acid fast bacilli gave negative results. Roentgenograms of the chest revealed an extensive suppurative process involving the entire right lung (fig. 101). Bronchographic studies demonstrated diffuse saccular bronchiectasis of the right lung. There was a small area of cylindric bronchiectasis in the left base. An attempt was made to examine the upper part of the esophagus with radiopaque oil but it was impossible for the patient to swallow enough oil to permit demonstration of anything. Apparently the upper part of the esophagus was completely closed. Barium was injected into the stomach through the gastric stoma and the lower part of the esophagus was visualized satisfactorily. A fistula from the esophagus to the right bronchus was demonstrated.

Esophagoscopy was attempted. There was scarring at the level of the cricoid cartilage. About 3 cm. below the cricopharyngeus muscle the esophagus narrowed to a tiny slit and it was impossible to pass the esophagoscope beyond that point. Bronchoscopy was then performed. A large amount of pus was seen coming from the right lung. There was considerable inflammatory reaction in the right main bronchus. The fistulous communication with the esophagus could not be visualized. Subsequently esophagoscopy was again performed and attempts were made to pass Siform bougies through the strictured esophagus but these failed.

* From Surgery, 23:221-226 (Feb.) 1948.



Fig. 101 —Extensive suppurative process throughout the entire right lung before operation.



Fig. 102.—Appearance after pneumonectomy and thoracoplasty on the right.

A cystoscope was inserted into the stomach through the gastric stoma and attempts were made to pass ureteral catheters up the esophagus. Complete obstruction was met about 8 to 10 cm above the cardia.

All attempts to open the esophagus having failed, it was decided that the patient should undergo surgical exploration. After thorough preparation, including administration of penicillin, operation was performed on October 10, 1946. A long curved incision was made around the tip of the scapula on the right. The fifth rib was resected and the pleura opened. The lung was densely adherent to the parietal pleura over its entire surface and was mobilized with some difficulty. In some places it was necessary to carry out the dissection along an extra-pleural line of cleavage. The hilar dissection was difficult but each vessel was dissected out individually, doubly ligated and sectioned. The posterior surface of the right main bronchus



Fig 103.—Appearance of the esophagus after closure of the fistula and progressive esophageal dilatations.

was densely adherent to the esophagus. The esophagus was so scarred that it was impossible to establish definitely the location of the fistula. The bronchus was severed, the lung removed and the stump of bronchus closed with a single row of interrupted silk sutures.

Below the level of the bronchus the esophagus appeared normal externally but when its lumen was opened several short strictured portions were observed; a ureteral catheter could be passed into the stomach, however. A cystoscope was inserted through the gastric stoma and the end of the ureteral catheter was picked up and brought out of the stomach through the gastric stoma. The esophagus above the bronchus was so scarred and fibrotic that it could hardly be recognized. A lumen was found finally and a ureteral catheter passed up toward the mouth. An esophagoscope was inserted and this catheter was picked up and brought out through the mouth. A strong silk fishline suture was attached to the ureteral catheter and one

ACUTE LARYNGOTRACHEOBRONCHITIS*

GEORGE B. LOGAN

"Acute laryngotracheobronchitis" is a descriptive pathologic term for a disease of varied bacterial origin. Despite its varied origin the symptom complex generally fits into a definite pattern because the symptoms are produced by inflammation or obstruction of one or more of the breathing passages.

In past times it was generally assumed—and correctly so—that a young child or an infant suffering from inflammation of the air passages or obstruction to breathing due to infection had diphtheria. That possibility should not be forgotten, as evidenced by the figures presented in another paper in this packet. Acute laryngotracheobronchitis, however, has been more common than laryngeal diphtheria in recent years. It has been shown to be due to hemolytic streptococci, *Streptococcus viridans*, *Staphylococcus aureus*, various pneumococci, *Haemophilus influenzae* and possibly on occasions to a virus.

The syndrome is seen in infants and children of all ages, but is more often a dangerous disease in children aged less than four years because of the relatively small size of the breathing passages. It is a disease most to be feared in those aged less than one year.

CLINICAL PICTURE

The symptoms at onset of the disease are usually the same as those of spasmodic croup: a harsh brassy cough and inspiratory stridor. These symptoms are generally due to subglottic edema, sometimes to supraglottic edema. Unless the vocal cords are involved the voice is not hoarse. Whatever the involvement of the region of the vocal cords, the classic signs of laryngeal obstruction are present: retraction above the suprasternal notch and clavicles, and of the epigastrium. Retraction of the intercostal spaces with inspiration is also often noted.

These symptoms at first may or may not be associated with fever. The absence of fever may correctly suggest that one is dealing with a case of spasmodic croup. However, my colleagues and I have seen several children whose dyspnea after an afebrile onset rapidly became very severe and who required tracheotomy within twelve to twenty-four hours after the onset. As the dyspnea increases, fever and evidence of toxicity usually appear.

If effective treatment is not instituted promptly death may take place.

PATHOLOGY

As the name implies, acute laryngotracheobronchitis is an acute inflammatory process involving the larynx, the trachea and the bronchi. Often edema is the only pathologic change noted. Secretion soon appears, especially in the lower part of the trachea and in the bronchi, and causes considerable mechanical obstruction to breathing. The secretion may be thick, ropy, gummy and tenacious, and frequently causes bronchial ob-

* From the Minnesota State Medical Association Speaker's Library Service: Child health, 1947, 3 pp.

struction and atelectasis. Multiple regions of atelectasis may be present. The secretion may become so thick as to form a cast of the tracheobronchial tree.

Inflammation and edema of the subglottic region are responsible for most of the symptoms of laryngeal obstruction.

TREATMENT

Acute laryngotracheobronchitis is best treated in a hospital, since tracheotomy or bronchoscopy or both frequently become necessary. If hospitalization is not possible, the patient can be treated in surroundings in which the air which he inspires can be highly moistened, if facilities for tracheotomy and constant nursing care are available.

A steam tent or steam room is usually the most effective means for supplying moist air. Two or three steam kettles are usually necessary to provide adequate humidity. The water should literally drip from the top of the tent or from the ceiling. The more modern mechanical humidifiers provide moisture without at the same time making the room uncomfortably hot. Oxygen should be well moistened if its use becomes necessary, since unmoistened oxygen exerts an undesirable drying effect on the secretion of the respiratory tract. Mechanical vaporizers may be used in conjunction with an oxygen tent. Lacking one of these, my colleagues and I recently have used two nebulizers. Distilled water was used as the fluid and an oxygen tank as the source of nebulizing force. In times past steam has been run into the oxygen tent by pipe or rubber hose. This method is cumbersome and unsatisfactory and may be dangerous. Moist cloths suspended in the partially filled ice compartment of an oxygen tent provide sufficient moisture to maintain the humidity at 70 to 80 per cent. The cloths must be moistened frequently.

We often employ sodium iodide or potassium iodide as an additional aid in liquefying tracheobronchial secretion. Five drops of a saturated solution of one of these salts may be given three times daily to a child of two years. Davison has contended that the use of medicines is unnecessary if the inspired air is properly moistened and that the medicine may make the patient nauseated. My colleagues and I agree but we have seen children who seemed to have been helped by the administration of one of the iodides.

It is essential that the patient's intake of fluid be maintained. If the patient cannot take fluids by mouth, they should be given by the intravenous or subcutaneous route. In dealing with young infants at least 2 fluidounces (60 c.c.) per pound (0.5 kg.) of body weight per twenty-four hours should be given and in dealing with older children about 1 fluidounce (30 c.c.) per pound (0.5 kg.). One or more small transfusions (25 to 150 c.c.) of blood may be necessary as a supportive measure and to aid in combating the infection. The administration of concentrated blood plasma or blood serum has been suggested for its dehydrating effect on the laryngeal edema. We have not had any favorable results from its use in the few instances in which it has been tried.

Food may be given according to the patient's desires. It is generally not desired during the acute phase except in liquid form.

Appropriate chemotherapy or antibiotic therapy varies from case to

case, depending on the etiologic bacterial agent. Penicillin at the present time is readily available and is effective when used to combat infections due to most strains of streptococci, staphylococci and pneumococci. It should be administered every two to three hours intramuscularly or by continuous intravenous infusion. Suggested dosage would be 200,000 units (divided into eight doses) daily for a two year old child. If penicillin in a heeswax-oil medium is employed it is wise to use 200,000 to 300,000 units daily.

It is very important that throat cultures be made and, if tracheotomy is done, that cultures of the tracheal secretions be made. Only rare strains of *Hemophilus influenzae* are killed by the use of penicillin. In fact one of the early uses of penicillin was to incorporate it in mediums on which *Hemophilus influenzae* was to be grown in order to kill off the other organisms which often overgrow it. *Hemophilus influenzae* infections respond well to the use of streptomycin. A total amount of 0.8 gm. daily is suggested, given intramuscularly in eight divided doses.

The sulfonamide drugs still are valuable therapeutic aids. *Hemophilus influenzae* infections often can be successfully treated with sulfadiazine, as can those due to streptococci, staphylococci and pneumococci. If sulfadiazine cannot be tolerated by mouth it may be given subcutaneously in the form of a 5 per cent solution of the sodium salt. The usual precautions regarding the use of the sulfonamide drugs must be observed.

Tracheotomy is indicated if the patient's dyspnea increases and if signs of laryngeal obstruction become more marked despite the use of moistening apparatus. Evidence of extreme restlessness, cyanosis and fatigue also is an indication for tracheotomy. In addition demonstration by auscultation that there is diminished entry of air into both lungs is further evidence that the patient's airway has been greatly reduced in caliber. Tracheotomy is generally preferred to intubation. Ideally it is done after bronchoscopic examination has been performed, after crusts and secretions have been sucked out through the bronchoscope and while that instrument is still in place.

After tracheotomy the air entering the tracheotomy tube must be kept moist; this aids greatly in the prevention of crusts that tend to form in the trachea. The same measures for moistening the air may be used postoperatively as preoperatively. My colleagues and I have found, however, that the use of a nebulizer as described by Albers is most satisfactory. A nebulizer is attached to a rubber tube that carries oxygen. The distal end is applied to the tracheotomy opening by means of a flexible rubber hose. Iams has reported that a small rubber nipple with the teat end cut off is satisfactory for this purpose. In our experience this measure has been lifesaving. If it is used, subsequent bronchoscopic aspiration is often unnecessary; the tracheal secretions can be aspirated by a catheter because they are kept moist.

Certain drugs are contraindicated in the treatment of acute laryngo-tracheobronchitis: (1) atropine, because of its undesirable drying effect; (2) codeine and morphine, for the same reason and also because the use of any sedative medication might obscure the indications for tracheotomy; (3) any other sedative drugs, and (4) either benadryl or pyribenzamine, because of the possible sedative effect and the occasional atropine-like action.

PENICILLIN AND STREPTOMYCIN AEROSOL THERAPY FOR CHRONIC BRONCHIECTASIS*

ARTHUR M. OLSEN

Bronchiectasis is a serious disease which merits the attention of all physicians. Since it often goes unrecognized in its early phases, a chronic cough always should be investigated carefully. A positive diagnosis of bronchiectasis can be made only after complete bronchographic studies, for the symptoms and even the roentgenogram of the chest cannot be relied on in making the diagnosis.

In chronic bronchiectasis the smaller bronchial tubes in the periphery of the pulmonary segments are dilated permanently. Cure can be effected only by removal of the segments of the lung that are involved. The symptoms of bronchiectasis are those of its complications. Secretions which accumulate in the dilated bronchi become infected and produce a chronic inflammatory process in walls of these bronchi. As a rule, the infection associated with bronchiectasis is nonspecific rather than specific. Thus many types of bacteria are found in the secretions which constantly form in these bronchi. The common bacteria which can be demonstrated in the sputum of these patients are listed in the tabulation.

TABULATION

COMMON PATHOGENIC BACTERIA FOUND IN BRONCHIECTATIC SECRETIONS

Gram positive	Gram negative
<i>Pneumococcus</i>	<i>Escherichia coli</i>
<i>Streptococcus</i>	<i>Hemophilus influenzae</i>
Hemolytic type	<i>Aerobacter aerogenes</i>
Nonhemolytic type	<i>Klebsiella</i>
<i>Staphylococcus</i>	<i>Pseudomonas aeruginosa</i>
<i>Micrococcus</i>	<i>Proteus</i>

The nonsurgical treatment of bronchiectasis includes the effective drainage of the infected secretions and the destruction of the bacteria in the secretions and in the bronchial mucosa. Postural drainage is a time-honored method of helping to eliminate purulent secretions from the bronchial tree and should be employed in every case of bronchiectasis. Bronchoscopic examination is of particular value in the exclusion of organic obstruction in the larger bronchi and temporarily helps the patient in his struggle to rid himself of the noxious secretions which constantly form in the infected bronchi. Antibacterial agents have assumed a definite place in the management of infected bronchiectasis. The oral and parenteral administration of sulfonamides and antibiotic preparations has proved of limited value in the reduction of the volume of infected bronchial secretions but certainly has aided in the prevention of complications following pulmonary resection for bronchiectasis. In recent months it has been demonstrated that the introduction of antibiotic preparations into the tracheobronchial tree is the most effective means of combating infection associated with bronchiectasis.

* From Minnesota Medicine. (In press.)

METHODS OF ADMINISTRATION OF ANTIBIOTIC AGENTS

The two principal methods by which solutions of penicillin or streptomycin can be introduced into the bronchi are as follows: Solutions may be instilled directly into the trachea through the bronchoscope, through a tracheal catheter, or by supraglottic instillation with a syringe and tracheal cannula. The other method consists in having the patient inhale a mist or aerosol of the solution. Both of these methods have their advantages and disadvantages.

In our experience direct instillation of antibiotic preparations into the bronchial tree is accomplished most satisfactorily by the supraglottic method. It usually is necessary to introduce 1 or 2 c.c. of a 5 per cent solution of cocaine into the trachea with a syringe and tracheal cannula. This procedure will provide sufficient local anesthesia to permit the patient to retain the solutions that will be instilled. Penicillin sodium is dissolved in physiologic saline solution in a concentration of 20,000 units per cubic centimeter and 5 or 10 c.c. of this solution is instilled slowly. When streptomycin hydrochloride has been used, it is dissolved in physiologic saline solution in a concentration of 0.1 gm. per cubic centimeter and, again, 5 to 10 c.c. may be employed. If the patient will lean either to the right or left side as he sits in his chair, the solution may be instilled into either side of the bronchial tree. If penicillin sodium and streptomycin hydrochloride are used, the solutions may be mixed and given at one time.

Supraglottic instillations may be given daily for many days. The success of this form of treatment depends on the ability of the patient to cooperate. It is desirable that instillations be given when the patient's stomach is empty. Postural drainage exercises should be carried out before each treatment. This method of treatment is much more effective when the patient is able to retain the solution for several hours than when he can keep it only a short time. Many patients are able to retain the solution without the benefit of local anesthesia.

Supraglottic instillations require some expertness on the part of the physician as well as the co operation of the patient. A large dose of penicillin or streptomycin or both may be given in a short time. For patients who have a large volume of purulent bronchial secretion, the supraglottic method has been effective, especially when employed as an adjunct to aerosol therapy. Disadvantages of the method are the frequent use of cocaine or a similar agent to produce local anesthesia and the fact that some patients are completely incapable of retaining the solutions.

Administration of nebulized antibiotic agents has been employed in nearly all of the cases of bronchiectasis treated at the Mayo Clinic. We have used either the Vaponefrin or DeVilbiss No. 40 nebulizer. Although we have tried the nebulizers equipped with large condensing bulbs or with rebreathing bags, we have returned almost invariably to the standard nebulizer because it is convenient and easy to handle. For hospital practice we have continued to use compressed oxygen as a source of positive pressure. For home treatment many patients have obtained small electric motors and air compressors or have used foot-operated air pumps.

We have been using penicillin sodium in concentrations ranging from 10,000 to 25,000 units per cubic centimeter. We usually give 200,000 to 400,000 units of penicillin daily. We have continued to use streptomycin

only in cases in which gram-negative organisms predominate in the sputum after a period of treatment with penicillin alone. In general, we find it desirable to mix streptomycin hydrochloride with penicillin sodium. Thus 200,000 to 400,000 units of penicillin and 0.5 to 1.0 gm. of streptomycin are dissolved in 16 to 20 c.c. of physiologic saline solution. Patients can nebulize 1 c.c. of solution in ten or fifteen minutes. Hospital patients are asked to nebulize 2 c.c. every hour for eight or ten hours each day.

PREOPERATIVE MANAGEMENT OF BRONCHIECTASIS

Bronchoscopic examination and complete bronchographic studies are carried out in all our cases of bronchiectasis in which pulmonary resection is considered. Before lobectomy or pneumonectomy is performed in the suitable cases, it is desirable that most of the iodized oil retained in the healthy lung tissue after bronchographic studies be coughed up or absorbed. Whenever possible, nebulization therapy is instituted in the waiting period. Penicillin is used routinely and streptomycin is used in cases in which gram-negative bacteria are found in the sputum. Daily supraglottic instillations are carried out in some cases. The length of preoperative treatment depends on the volume of purulent secretions and the amount of lung tissue to be resected. Patients who have bilateral involvement are given a much longer course of preoperative treatment. In the usual case in which bronchiectasis is confined to one lobe, five to seven days of preoperative treatment is adequate. In the forty-eight hours prior to operation our patients now receive large doses of penicillin by intramuscular injection. Postural drainage exercises are employed in all cases.

It has been our definite impression that the preparation of patients for lobectomy with penicillin aerosol has been most helpful in preventing postoperative complications. Although in occasional cases empyema occurs, the incidence of complications following pulmonary resection for bronchiectasis has been very low.

NONSURGICAL MANAGEMENT OF BRONCHIECTASIS

Unfortunately, many patients who have bronchiectasis are not suitable candidates for pulmonary resection. These patients often are the ones who are most desperately in need of help. Frequently they are dyspneic and chronically ill and have disease of the accessory nasal sinuses. Their sputum often has a foul odor and they are virtual outcasts from society.

No treatment will cure these individuals of their bronchiectasis. From experience we know that sufficient rest and good nutrition, a favorable climate and regular postural drainage will help them to control the bronchorrhea. Aerosol therapy has been of great benefit in a good many of these cases. However, a much longer period of intensive treatment is required than in the preoperative cases. Most of our patients have been hospitalized for their initial course of treatment, which may last from two to six weeks. Inhalation treatment with penicillin is started on admission. Stains and cultures of the sputum are made twice a week. An accurate chart of the daily volume of sputum is kept and notations are made of character and odor of the secretions. Postural drainage is carried

METHODS OF ADMINISTRATION OF ANTIBIOTIC AGENTS

The two principal methods by which solutions of penicillin or streptomycin can be introduced into the bronchi are as follows: Solutions may be instilled directly into the trachea through the bronchoscope, through a tracheal catheter, or by supraglottic instillation with a syringe and tracheal cannula. The other method consists in having the patient inhale a mist or aerosol of the solution. Both of these methods have their advantages and disadvantages.

In our experience direct instillation of antibiotic preparations into the bronchial tree is accomplished most satisfactorily by the supraglottic method. It usually is necessary to introduce 1 or 2 c.c. of a 5 per cent solution of cocaine into the trachea with a syringe and tracheal cannula. This procedure will provide sufficient local anesthesia to permit the patient to retain the solutions that will be instilled. Penicillin sodium is dissolved in physiologic saline solution in a concentration of 20,000 units per cubic centimeter and 5 or 10 c.c. of this solution is instilled slowly. When streptomycin hydrochloride has been used, it is dissolved in physiologic saline solution in a concentration of 0.1 gm. per cubic centimeter and, again, 5 to 10 c.c. may be employed. If the patient will lean either to the right or left side as he sits in his chair, the solution may be instilled into either side of the bronchial tree. If penicillin sodium and streptomycin hydrochloride are used, the solutions may be mixed and given at one time.

Supraglottic instillations may be given daily for many days. The success of this form of treatment depends on the ability of the patient to cooperate. It is desirable that instillations be given when the patient's stomach is empty. Postural drainage exercises should be carried out before each treatment. This method of treatment is much more effective when the patient is able to retain the solution for several hours than when he can keep it only a short time. Many patients are able to retain the solution without the benefit of local anesthesia.

Supraglottic instillations require some expertness on the part of the physician as well as the co-operation of the patient. A large dose of penicillin or streptomycin or both may be given in a short time. For patients who have a large volume of purulent bronchial secretion, the supraglottic method has been effective, especially when employed as an adjunct to aerosol therapy. Disadvantages of the method are the frequent use of cocaine or a similar agent to produce local anesthesia and the fact that some patients are completely incapable of retaining the solutions.

Administration of nebulized antibiotic agents has been employed in nearly all of the cases of bronchiectasis treated at the Mayo Clinic. We have used either the Vaponefrin or DeVilbiss No. 40 nebulizer. Although we have tried the nebulizers equipped with large condensing bulbs or with rebreathing bags, we have returned almost invariably to the standard nebulizer because it is convenient and easy to handle. For hospital practice we have continued to use compressed oxygen as a source of positive pressure. For home treatment many patients have obtained small electric motors and air compressors or have used foot-operated air pumps.

We have been using penicillin sodium in concentrations ranging from 10,000 to 25,000 units per cubic centimeter. We usually give 200,000 to 400,000 units of penicillin daily. We have continued to use streptomycin

only in cases in which gram-negative organisms predominate in the sputum after a period of treatment with penicillin alone. In general, we find it desirable to mix streptomycin hydrochloride with penicillin sodium. Thus 200,000 to 400,000 units of penicillin and 0.5 to 1.0 gm. of streptomycin are dissolved in 16 to 20 c.c. of physiologic saline solution. Patients can nebulize 1 c.c. of solution in ten or fifteen minutes. Hospital patients are asked to nebulize 2 c.c. every hour for eight or ten hours each day.

PREOPERATIVE MANAGEMENT OF BRONCHIECTASIS

Bronchoscope examination and complete bronchographic studies are carried out in all our cases of bronchiectasis in which pulmonary resection is considered. Before lobectomy or pneumonectomy is performed in the suitable cases, it is desirable that most of the iodized oil retained in the healthy lung tissue after bronchographic studies be coughed up or absorbed. Whenever possible, nebulization therapy is instituted in the waiting period. Penicillin is used routinely and streptomycin is used in cases in which gram-negative bacteria are found in the sputum. Daily supraglottic instillations are carried out in some cases. The length of preoperative treatment depends on the volume of purulent secretions and the amount of lung tissue to be resected. Patients who have bilateral involvement are given a much longer course of preoperative treatment. In the usual case in which bronchiectasis is confined to one lobe, five to seven days of preoperative treatment is adequate. In the forty-eight hours prior to operation our patients now receive large doses of penicillin by intramuscular injection. Postural drainage exercises are employed in all cases.

It has been our definite impression that the preparation of patients for lobectomy with penicillin aerosol has been most helpful in preventing postoperative complications. Although in occasional cases empyema occurs, the incidence of complications following pulmonary resection for bronchiectasis has been very low.

NONSURGICAL MANAGEMENT OF BRONCHIECTASIS

Unfortunately, many patients who have bronchiectasis are not suitable candidates for pulmonary resection. These patients often are the ones who are most desperately in need of help. Frequently they are dyspneic and chronically ill and have disease of the accessory nasal sinuses. Their sputum often has a foul odor and they are virtual outcasts from society.

No treatment will cure these individuals of their bronchiectasis. From experience we know that sufficient rest and good nutrition, a favorable climate and regular postural drainage will help them to control the bronchorrhea. Aerosol therapy has been of great benefit in a good many of these cases. However, a much longer period of intensive treatment is required than in the preoperative cases. Most of our patients have been hospitalized for their initial course of treatment, which may last from two to six weeks. Inhalation treatment with penicillin is started on admission. Stains and cultures of the sputum are made twice a week. An accurate chart of the daily volume of sputum is kept and notations are made of character and odor of the secretions. Postural drainage is carried

Such a procedure will frequently reveal unexpected and interesting findings. It is important in cases of this type, if the full value of the operation is to be attained, that the tissue or secretion which is removed be examined by a competent pathologist.

Since time immemorial, pathologic processes have been shrouded with varying degrees of mysticism. With the development of the concept of cellular pathology and with an appreciation of physiologic mechanisms a more rational approach has been made to the understanding of diseases. However, cellular pathology rests exclusively on a morphologic basis, and interpretations and opinions concerning such pathologic processes as may be observed grossly and microscopically are limited to one's ability to appreciate and recognize varying degrees of morphologic change. In the field of oncology various procedures have been developed by which one may not only recognize the nature of the tumor but may also express an opinion as to the rapidity of growth with a view to prognosticating the outcome of the disease.

With the growth of the cellular theory of pathology, techniques have been developed by which the tissues to be examined are either killed by some suitable fixing agent, such as formalin or mercuric chloride, or are frozen in the fresh state so that an immediate histologic preparation may be made. The former method kills not only all the tissue cells but also the microbe agents which may be the cause of the lesion. In the second method, the handling of tissues preparatory to making the frozen section results in contamination so that a suitable bacteriologic examination may be impossible should the histologic study reveal the desirability of such examination.

Because many different infectious diseases produce histologic patterns which grossly simulate one another, it becomes the duty and the responsibility of the pathologist to be prepared to establish the nature of the etiologic agent inducing any inflammatory processes which he considers unlikely to be a part of, or related to neoplastic changes. While modern pathologists recognize the importance of consulting with bacteriologists or of making their own bacteriologic examinations, concerning certain inflammatory processes it should be emphasized that a bacteriologic examination should supplement, not replace, the histologic study, since malignant lesions may be secondarily infected and may simulate an infectious granuloma. We have found it of value to handle all thoracic surgical specimens and material for biopsy in such a manner that satisfactory bacteriologic examinations may be made in the event an inflammatory process is encountered; thus we avoid subjecting the patient to the expense and inconvenience of a repeated biopsy. The importance of such supplementary aid to the clinician and pathologist is exemplified in the following cases.

REPORT OF CASES

Case 1.—A woman forty-two years of age who resided in Oklahoma presented herself at the Mayo Clinic for examination on August 10, 1946. She gave a history of rheumatic pains which had been present for four years. Her primary reason for seeking medical attention at that time was to learn the nature of a questionable lesion in the pelvis.

At the time of examination the patient was found to have a small uterine fibroid. The fibroid was of such size and character that surgical intervention did not seem indicated. During the

course of a general examination a roentgenologic examination of the chest revealed a discoid or globular mass lying just subcostal to the posterior portion of the tenth rib on the left side (fig. 104). This was suggestive, to the roentgenologist, of either a benign tumor or an inter-



Fig. 104 (case 1).—Circumscribed tumor mass in left base.



Fig. 105 (case 1).—Gross appearance of tumor removed.

costal neurofibroma. Results of examination of the sputum for acid fast organisms were reported as negative. The urinalysis, hemoglobin determination, erythrocyte and leukocyte counts, and determination of the sedimentation rate gave values which were within normal limits, the reaction to flocculation tests for syphilis was negative.

From the history and the information at hand, it was felt that the condition might be a hamartoma although the possibility of malignancy could not be excluded. Exploratory thoracotomy seemed advisable in this case and the patient was so advised. At operation on October 29, 1946, a firm, rounded tumor mass was found situated near the periphery of the lower lobe of the left lung. This mass was excised. The specimen removed was reported by the pathologist as having the gross and microscopic appearance suggestive of healed primary tuberculosis (fig. 103). Material from the tumor mass was injected into guinea pigs in order to determine definitely the underlying etiologic agent. Much to our surprise, when the animals were examined at necropsy eight weeks later they were found to be infected with *Coccidioides immitis* and there was no evidence of tuberculosis. Because of this report, the original tissue was re-examined and additional sections were taken from the tumor mass; at this time numerous small spherical bodies were recognized. Some of these bodies appeared to be in the budding form, but none could be found which had the endosporeulating spherules characteristic of coccidioidomycosis.

In retrospect, the diagnosis of this lesion might have been made if a skin test for coccidioidomycosis had been carried out. However, the clinical history and the fact that the patient came from a part of the country where coccidioidomycosis is not endemic did not arouse our suspicion of a coccidioidomycotic infection. The case does emphasize the importance of keeping the possibility of coccidioidomycosis in mind in all cases of pulmonary infiltration. Although surgical intervention is not recommended as a routine procedure in coccidioidomycosis, it is of interest that this patient made very satisfactory progress after the removal of the coccidioidal nodule from her lung. It is, of course, problematic whether the improvement in her general rheumatic pains can be justifiably ascribed to the removal of this nodule.

Case 2.—A woman forty-six years of age who came from Minnesota was admitted to the clinic September 18, 1946. Her chief complaint was that of cough and expectoration. She stated that her difficulty began after an attack of pneumonia in 1919. Since that time she had suffered from a chronic cough and had been subject to frequent pulmonary infections. For the past five years she had coughed up a great deal of purulent secretion; the quantity varied from a half teaspoonful to a half cupful in twenty-four hours. After overexertion the sputum had at times been blood streaked. During the past year the patient had noted an increasing degree of dyspnea associated with exertion.

On physical examination the only essential findings were a slight limitation in movement of the right side of the chest on respiration and a few coarse rales heard over the right lower and middle lobes. When the patient was tipped over she expectorated a characteristic bronchiectatic type of sputum. Roentgenologic examination of the chest was reported as showing probable contraction of the right lower lobe (fig. 106). Sputum examination did not reveal acid-fast organisms. Bronchoscopic examination was performed and a large amount of purulent secretion was found coming from the bronchi of the right lower and middle lobes. The mucous membrane of the bronchus of the right lower lobe was markedly inflamed. No evidence of a tumor or stenosis of the bronchus was seen. Bronchograms were made the following day; these showed evidence of bronchiectasis involving the right lower and middle lobes (fig. 107).

A diagnosis of bronchiectasis involving the right lower and middle lobes was made and operation was advised. After preoperative nebulization with penicillin the patient was operated on on October 26, 1946. The middle lobe was found to be completely collapsed. A right middle and lower lobe lobectomy was performed. On gross and microscopic examination the pulmonary tissue removed showed the characteristic appearance of bronchiectasis with associated pneumonitis (fig. 108a). Since pneumonitis is a common finding in bronchiectasis, in this case it was not thought necessary to carry out further pathologic or bacteriologic studies to determine the etiology of this lesion.

After the operation collapse of the right upper lobe developed. In spite of repeated bronchoscopic aspirations the right upper lobe failed to re-expand. It became necessary to perform a right upper lobe lobectomy in December, 1946. The gross and microscopic appearance of the right upper lobe was the same as that found in the right lower and middle lobes at the time of their removal, except that the degree of bronchiectasis was less marked (fig. 108b). The material



Fig. 106 (case 2).—Contraction of right lower lobe.

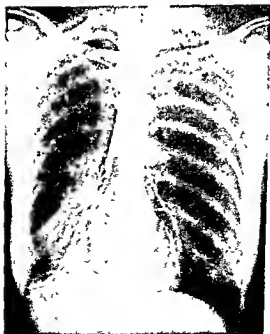


Fig. 107 (case 2).—Bronchiectasis of right lower and middle lobes.

removed at this time was subjected to bacteriologic examination and was found to contain *Pasteurella* of the animal variety. Empyema of the right side of the chest developed after the right upper lobe lobectomy; drainage was obtained by open operation. Although the *Pasteurella* in this case was found to be resistant to streptomycin *in vitro*, the antibiotic agent was instilled into the empyema pocket with apparent benefit.



Fig. 108 (case 2).—a. Section of right lower lobe ($\times 3$); b. section of right upper lobe ($\times 3.5$).

There might be some question as to whether the *Pasteurella* infection in this case was primary or secondary in nature. In any case, it is unusual that the involvement of the upper lobe should have occurred after the lower and middle lobe lobectomy and that the pathologic process found in all three lobes was identical in nature. It would seem that the *Pasteurella* was the underlying etiologic factor in this case.

Case 3.—A man thirty-two years of age whose home was in Mexico came under our care on September 26, 1946, stating he had cancer of the lung. He said that he had enjoyed good health until May, 1946, when he first noticed a sharp pain in the left side of the chest. The pain was not related to respiration and lasted but three days. With the onset of the chest pain he noted



Fig. 100 (case 3) —Lesion in left lower pulmonary field



Fig. 110 (case 3).—Mass removed at operation.

an elevation of temperature to 40.5° C. Roentgenologic examination of his chest at that time was reported as disclosing evidence of an area of infiltration which involved the left lower lobe, and which led to a diagnosis of congestion of the left lower lobe. The patient was treated with injections of penicillin without apparent improvement. His temperature remained elevated for twenty-one days. Since the onset of illness the patient had lost weight. He had had a very slight, unproductive cough. Because the roentgenograms of the chest failed to show evidence of any improvement, carcinoma of the lung was suspected and the patient was referred to us for treatment.

The patient was found to be a well-developed, healthy-appearing man with normal blood pressure, pulse and temperature. Physical examination of the chest gave essentially negative results. Urinalysis, hemoglobin determination, erythrocyte and leukocyte counts and differential count gave results which were within normal limits and the reaction to the flocculation test for syphilis was negative. It was impossible to obtain sputum for culture or microscopic examination for tuberculosis or for examination for malignant cells. A roentgenogram of the chest made on September 27, 1946, showed evidence of a lesion in the left lower pulmonary field which was partially obscured by the left side of the heart (fig. 109). The lesion was considered by the roentgenologist to be probably a hamartoma. Bronchoscopy was done and gave entirely negative results. The history of pulmonary difficulty of four months' duration, with loss of weight and a persistent nonresolving chest lesion as seen on roentgenologic examination, made the diagnosis of carcinoma very probable.

Exploratory thoracotomy was advised. The patient was operated on on October 26, 1946, and a lesion was found situated in the inferior portion of the left upper lobe which appeared to be inflammatory in nature. It was adherent to the pericardium as well as to the chest wall. A left upper lobe lobectomy was performed. The specimen removed was reported by the pathologist as being a granulomatous inflammatory mass, possibly a lesion of coccidioidomycosis (fig. 110). However, no endospore-forming spherules were found although budding forms were present, suggesting the possibility of blastomycosis. Bacteriologic studies of the tissue revealed large numbers of *Coccidioides immitis*; no blastomycetes were recovered in the culture, although their presence had been suggested by the appearance of the budding forms in the microscopic examination. Coccidioidin skin tests were done after operation, and the results were found to be positive.

In this case, the possibility of coccidioidomycosis should undoubtedly have been suspected before operation; however, this disease was not suspected and it was necessary for the bacteriologist to have special studies carried out in order to permit determination of the exact cause of the patient's difficulty. This patient did very well after operation.

Obviously, it should be our cherished goal to try to establish a positive clinical diagnosis in every case of pulmonary disease. Careful and diligent use must be made of the many helpful tests and examinations that are available for this purpose. The close co-operation of the roentgenologist, bronchoscopist, bacteriologist and other specialists is highly important. Despite all this, there will remain a goodly number of patients suffering from pulmonary disease in whom a positive diagnosis cannot be arrived at. It is often unwise, in a case of this type, to procrastinate too long with periods of observation or with tests that require many weeks for completion, because of the danger that the lesion may be malignant in nature, thereby requiring prompt treatment if it is to be eradicated successfully. In properly selected cases of this type, exploratory thoracotomy is often indicated; the pathologist can often furnish a prompt explanation of the underlying cause of the pulmonary lesion. In cases in which the cause is uncertain, bacteriologic studies of the tissue should be employed, as often useful information which might otherwise escape detection may be obtained by this method.

PULMONARY RESECTION FOR ABSCESS OF THE LUNG*

ROBERT P. GLOVER AND O. THERON CLAGETT

In thirty-seven cases primary lung abscess in various stages of chronicity was treated by pulmonary resection. The elapsed time from the original diagnosis to surgical excision averaged eighteen months. In the twenty-one cases in which a conservative resection (lobectomy or less) could be performed, there was one death (mortality rate 4.8 per cent) despite the wasting and general debility of the patients when admitted for treatment. In the remaining twenty cases the results were good and are regarded as asymptomatic cures. In contrast, of the sixteen cases in which total pneumonectomy was performed, in only seven was a good result obtained, and in three of these it was delayed considerably by complications. There were six deaths attributable to operation (mortality rate 37.5 per cent), and three late deaths resulting from brain abscess.

We believe that if the problem of acute lung abscess is considered as surgical from the outset and the optimal time for intervention is recognized and acted on with dispatch, the problem of chronic lung abscess will be virtually eliminated. Until such a time pulmonary resection is the treatment of choice for suppuration of long standing. It is our opinion that bronchographic follow-up of patients treated by open drainage will reveal that a significant number are left with residual parenchymal and bronchiectatic changes, which in all probability will lead to further symptoms at some future date. This is especially true when abscesses are drained in the chronic state or after secondary changes have taken place. For this reason pulmonary resection should take preference over open drainage in most cases seen by the surgeon at the present time.

INCIDENCE OF PULMONARY EMBOLISM AFTER VENOUS SCLEROSING THERAPY†

FREDERICK L. SMITH AND MARCELLUS A. JOHNSON, III

In a statistical review of the records of postmortem examinations at the Mayo Clinic over a ten year period, 1917-1926, Henderson found 313 cases of pulmonary embolism; 267 of these were surgical cases and forty-six were nonsurgical. In 223 (83.5 per cent) of the cases the emboli were the primary cause of death. The average age of the patients was 53.2 years. Nineteen of the forty-six nonsurgical cases were cases of cardiovascular disease. The source of emboli was most commonly in the iliac, femoral or pelvic veins, prostatic plexus or vena cava in the order named. We believe that the incidence of fatal pulmonary embolism has decreased in recent years. Other studies have revealed this decrease. Some of the reasons for this decrease are as follows:

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Anticoagulants have been introduced to forestall an acute or remote possibility of pulmonary embolism. Their proper use is well described by Allen, Barker and Hines. The value of anticoagulant therapy is clearly indicated by the report of Barker and his associates on 1,000 specially selected surgical patients who were given dicumarol in the immediate postoperative period. In the entire series only one death occurred from pulmonary embolism. This extremely low incidence of fatal pulmonary embolism is remarkable because 379 patients had demonstrated a thrombotic tendency at some time before operation and 438 had been subjected to abdominal hysterectomy. The statistical risk of thrombosis and embolism in abdominal hysterectomy is known to be high. One of us (F. L. S.) in an unpublished study on postoperative complications made in 1919 also observed this high incidence following abdominal hysterectomy.

The surgical interruption of the femoral vein was recommended for pulmonary embolism by Homans in 1934 and from 1941 on, in the medical service of the Massachusetts General Hospital, ligation became the treatment of choice but it usually was performed only on the affected side. In 1943, bilateral interruption regardless of noninvolvement of the other extremity became the routine treatment of pulmonary embolism on that service. By the last procedure Carlotti and his associates at the Massachusetts General Hospital reduced the mortality rate from pulmonary emboli in the medical cases in the years 1941 to 1945 to 28.3 per cent as compared to 50.7 per cent in medical cases in which this procedure was not carried out after a nonfatal episode of pulmonary embolism.

In cases in which sclerosing treatment of varicose veins is planned at the Mayo Clinic, special care is taken in examining the extremities for evidence of vascular disease and in eliciting a history of any previous episodes which could be interpreted as being due to vascular disease of the lower extremities. Often localized atrophy, with brawny induration and discoloration, or slight edema of the leg suggesting some previous episode of thrombophlebitis is found. At the time this episode occurred, it often was not considered of any special significance by the patient or physician, if consulted, but was passed off as extraneous. Sometimes a patient who has had previous sclerosing treatment of a vein may volunteer the information or respond to a question to the effect that a few days following this treatment he had awakened at night "with a touch of pleurisy," had had difficulty in breathing or possibly had had rusty expectoration for which he took some aspirin, applied a mustard poultice to the affected side or remained in bed for a few days. In all probability an embolic episode was the source of the trouble. Doubtless many more respiratory episodes of this type occur after sclerosing treatment than are reported. This failure is due to lack of understanding of the true condition. The embolic accident when it does occur may be due directly to sclerosing treatment, or possibly its occurrence is a coincidence and previous episodes have followed an ancient thrombophlebitis.

Special care is taken in cases in which previous episodes or some indication of vascular disease is obtained. In our experience in sclerosing treatment of varicose veins at the Mayo Clinic we have found that the massive type of embolus is seldom encountered in such cases but rather small emboli occur which involve the lungs in varying degrees. A shotty

appearance in the base of one or both lungs may be evident in the roentgenogram.

From 1927 through June 30, 1947, 11,700 patients have been treated for varicose veins at the Mayo Clinic and only seventeen of these patients (0.14 per cent) have had pulmonary emboli. Sixteen had nonfatal emboli and recovered without subsequent sequelae and one had a fatal embolus. Prior to March, 1937, treatment in our series consisted mainly of injections. After 1937 the combined ligation and injection technic was used; this technic consists of injection of sclerosing solution into the distal segment at the time of ligation of the great or small saphenous vein. Our yearly reports reveal that from 80 to 88 per cent of all patients were treated by the above procedure and the remainder received injections only. In 93 per cent of the cases in which operation was performed, the great saphenous vein and its tributaries were ligated and in 7 per cent the small saphenous vein was ligated in the popliteal space.

We have attempted to determine whether the seventeen patients who had pulmonary emboli had any characteristics which distinguished them from the patients whose course was uncomplicated. All seventeen were referred for venous therapy after complete examination. There were nine men and eight women. Their average age was fifty years. Three had mild hypertensive disease, one had duodenal ulcer, one localized lupus erythematosus and one slight pneumoconiosis. One gave a history of deep thrombosis of the femoral vein ten years previous to coming to the clinic but complete involution had occurred before examination in the section on venous therapy. Varicose veins had been present for an average of twenty-seven years in the seventeen cases and the average length of time during which discomfort had been manifest was six years. Four patients had varices on one lower extremity only and thirteen had them on both lower extremities. Six had varicose ulcers. In six cases the embolic episode developed prior to 1937, whereas after 1937 when ligations were instituted, eleven occurred. In these eleven cases combined ligation and injection was employed.

The sclerosing solution used for the most part in our entire series was a 5 per cent solution of sodium morrhuate although a 10 per cent solution was used when a more concentrated solution was required. Quinine and urethane (Génévrier's solution), a solution of 30 per cent glucose and 25 per cent salt, 30 and 40 per cent solutions of sodium salicylates and 20 per cent solution of salt were all used early in the work but sodium morrhuate proved to be the solution of choice.

Always to identify patients during the treatment period who are likely to develop an embolic condition is practically impossible as all exhibit swelling and tenderness with local increase of heat resulting from the chemical endophlebitis. Occasionally chills and fever with moderate to high leukocyte count will be observed; this episode lasts for twenty-four hours or so and then the leukocytosis recedes. The local tenderness and swelling may last for some days. Their duration depends on the size of the vein treated. Our earliest embolic episode was four days and our latest sixteen days after beginning of treatment. In fifteen cases roentgenograms showed sufficient evidence to warrant a diagnosis of embolism with ensuing infarction.

Just what initiates the development of a thrombus is a matter of conjecture and in the literature reviewed various explanations were advanced. Investigators are generally agreed that the basic principle on which they have been working is the prevention of formation of thrombi in the deep veins of the lower extremities. Enough information has been gathered to attribute the formation of a thrombus in many cases to operative procedures. Allen and Linton reported that debilitated persons with restricted mobility of the lower extremities are likely to have thrombosis. Yet Munro in discussion of Albright's paper stated that in the army general hospitals in England pulmonary embolism rarely occurred in 250 cases in one series and in 500 in another in which patients paralyzed because of injury to the spinal cord were confined to bed and their legs were immobile for months. Thrombosis is prone to develop in association with trauma and infections. All investigators have observed the increased incidence of thrombosis in patients more than forty years of age.

It is difficult to determine why an embolus develops during active sclerosing treatment. Chemical endophlebitis should anchor the thrombus at the site of the injection. Tributary communicating veins may be a factor, for phlebothrombosis may develop in them although the walls of the veins may not be affected, and some muscle contraction may express the soft jelly-like clot into the deep circulation. Necropsy has revealed that clots had formed during life and propagated rapidly toward and into the large veins with no evidence of injury to the vein walls but simply with stasis or stagnation of circulating blood.

Inasmuch as thrombophlebitis of the lower extremities is the main factor, in surgical procedures regardless of the site of the operation, patients who have undergone injection treatment and operation, especially those confined to bed, should have leg and foot exercises at frequent intervals and, when physical condition permits, actual walking is beneficial.

Before the days of anticoagulants, at the clinic we hospitalized not once patients who had pulmonary emboli after sclerosing treatment, placed them in the Fowler position and immobilized the chest as much as possible with binders and by the hypodermic use of morphine sulfate every four hours until the respiratory rhythm was reduced to 10 or 12 per minute; enough sedation was given to keep the patient in a semicomatose state and an oxygen tent containing a mixture of 50 per cent oxygen with the air was employed. The oxygen compensated for the low volume intake and also more or less prevented pulmonary abscess or bronchiectasis if these did not previously exist. We found that if the patients with a severe involvement did not die in twenty-four hours, they recovered.

It is now our practice to hospitalize any patient who is suspected of threatening venous clotting as a prophylactic measure and to begin anticoagulant therapy immediately. If the consultants on the vascular service advise operation because of likelihood of a thrombotic migration from thrombophlebitic involvement in the extremity, the region of the deep veins of the extremity is explored and ligation is performed.

THE ROLE OF PLEURAL EXUDATION IN INFECTION FOLLOWING PNEUMONECTOMY: AN EXPERIMENTAL STUDY*

JOHN T. SMALL AND GEORGE M. HIGGINS

Pulmonary resection, without surgical collapse of the thoracic wall as in thoracoplasty, produces a large surgical dead space, a condition which would not be encountered in the abdomen with its collapsible walls. The immediate and sustained reaction of the organism to pneumonectomy is obliteration of this space by a combination of factors which include (1) the overdistention of the remaining lung tissue, (2) the retraction of the parietes and (3) the production of a fluid exudate. The later effects of pneumonectomy in lower animals cannot be compared to those in man since the patulous mediastinum in the former permits a gradual and complete expansion of the remaining lung which eventually fills the space. However, the early phenomenon of exudation is similar in both lower animals and man and appears presumably as a universal expression of irritation or a changed environment for the mammalian pleural membrane.

Packing the pleural cavity after removal of the lung with an inert nondistensible material such as gelatin foam serves to restore the remaining parietal pleura to a more nearly normal pressure status. Under such conditions the effusion which normally occurs after pneumonectomy is greatly inhibited but not completely suppressed and the cellular response in both pleural membranes as well as the exudate is but expressive of a mild inflammatory reaction. On the other hand, the cytologic change of the exudates and the histologic change of the pleural membranes which ensues on pneumonectomy without gelatin foam packing indicate an extremely high degree of irritation in the pleura. These pleural reactions appear to be comparable to changes which accompany bacterial or other forms of inflammation. The exudate produced by pneumonectomy was invariable in its time of appearance and the chemical, microscopic and gross changes were always consistent and predictable. The closure of the thorax, followed by the regulation of the intrathoracic pressure to a constant level in pneumonectomized animals has assured a set of regular conditions for the involved pleura, an adjustment which cannot be attained in clinical investigation owing to the varying ages and varying pathologic states of the subjects. The pleural irritation which follows pneumonectomy appears to be on a purely mechanical basis and is not modified by buffering capacity of tissue, the pH, lymphatic blocking or concentration of electrolytes. These are variables which need to be considered when various irritants are placed in the pleural space after operation.

The classic theory for the origin of a pleural effusion is not applicable to the effusion which follows pneumonectomy, for these older studies eliminate the role of the parietal pleura and consider only the visceral pleura of dead animals *in vitro*. We were unable to find either gross or microscopic evidence that the visceral pleura of the remaining lung had taken part in the production of these pleural effusions. Graham's use of the concept of a changing negative pressure around the visceral pleura

* Abridgment of paper published in full in *Surgery*. (In press)

serves to emphasize the common misconception that such a negative pressure is in some manner essential to the performance of respiration, in which act it becomes still more negative. In senile emphysema or in the newborn mammal the lungs completely fill the pleural space, are almost lacking in elastic tissue and do not collapse to any extent when the thorax is opened.

Small amounts of exudate were observed regularly when a simple pneumothorax was done and the cytologic picture of the resulting exudate resembled that found after pneumonectomy. The differences were only quantitative and were further expressed by the changes in total leukocyte level of the circulating blood. When the exudate was relatively large in amount, the appearance of a large number of blood leukocytes in the exudate was coincident with a drop in total number of leukocytes in the blood. This relationship substantiates the earlier work of Lippmann and Plesch who found no granulocytic cells in the exudates which formed from the irritated pleurae of animals whose circulating granulocytes had been destroyed with thorium X and indirectly shows the source of these cells from the circulating blood.

The granulocytic infiltration into the pleura thus represents the early phase of the pleural reaction to pneumonectomy. This phase is soon followed by the appearance in the exudate of large numbers of mononuclear leukocytes. This sequence of neutrophilic polymorphonuclear leukocytes, followed by an infiltration of mononuclear phagocytes, is the classic picture of the successful response to any inflammatory condition, be it bacterial or otherwise. These data do not sustain the views that either the microphage or the macrophage is the essential element in an inflammatory response but do establish the fact that the pleural response to injury is essentially similar to that observed in the reputedly more resistant peritoneum. The introduction of irritating substances into the pleural space has been shown to produce exudates which are large in volume but low in their cellular contents. The presence of inflammatory cells has been shown by passive transfer experiments to be essential for the destruction of bacteria and we have observed that exudates, low in cellular content, were invariably associated with an increased percentage of mortality and morbidity.

The hypoproteinemia which follows anesthesia and any surgical trauma was marked after pneumonectomy. No doubt this was partly due to the fact that the supply of circulating protein was tapped in order to provide for the cells and serum of the exudate accumulating in the pleural space. Such hypoproteinemia has not been shown to be inconsistent with satisfactory healing in the otherwise healthy animal but it would seem rational to correct a too greatly prolonged hypoproteinemia in the debilitated human being. The placing of isotonic solutions such as plasma, certain blood substitutes or various drugs in the pleural space after pneumonectomy did not obviate the lower plasma protein levels. Furthermore these solutions invariably contributed to a dilution of the cellular elements which are required to combat contamination and to facilitate the repair process.

There was no depletion of the total number of erythrocytes or of the hemoglobin levels up to seventy-two hours after pneumonectomy, provided the animal was healthy and came to operation with a normal quota

of these blood elements. At the later periods, however, we have observed significant declines in these measurements, which persisted for as long as six months.

Normal pleural fluid contains large numbers of cells which are recognized as the totipotent components of the so-called reticulo-endothelial system, the function of which is so largely related to reparative processes. This may presumably explain the known clinical and experimental facts which show conclusively that the intact pleural membranes without pneumothorax, are capable of resisting heavy assaults. The high levels of leukocytes which exist within these normal fluids, place them far from the conventional category of a mere thin film of lymph which acts as a lubricant. If we are to regard the total leukocyte level in the circulating blood as an indication of the ability of the organism to combat or respond to an infection, then the enormous number of such cells within normal pleural fluid is certainly not without significance. Earlier studies on the peritoneal fluid of albino rats have shown that a leukocyte level is maintained there which compares very well with the large number of such cells found in the pleural fluids. Furthermore, studies on the differential distributions have shown that the cellular components within the two fluids have almost an exact ratio to one another. The total leukocyte levels in the peritoneal and pleural fluids of the various species appear to be quite parallel to the known natural resistance which these common laboratory animals have attained. The rat is notoriously resistant to an infection of the thorax or abdomen and its almost complete resistance to the tubercle bacillus is a most arresting fact when we compare the leukocyte count of its pleural fluid with that of the more susceptible dog.

The consistent character of the postpneumonecrotic exudates, under the controlled conditions of the experimental procedures, was correlated with the histologic responses in the various pleural regions. The left diaphragmatic and the lower costal pleurae were found to be irritated in a manner similar to the parietal pleura, until such time as the effusion developed and apparently protected these structures from the irritating influences of the oscillating pressures incited by the respirations of the remaining lung.

The most marked and progressive changes were observed in the mediastinal pleura. In each animal in which the inert packing of gelatin foam had been inserted in the pleural space for more than forty-eight hours there was a definite fibrinous attachment of the mass to the mediastinal pleura. This attachment was not observed on the costal or diaphragmatic surfaces until much later. At forty-eight hours, the fibrin content of the exudate, as seen in smears, had definitely increased, although quantitative estimations of fibrin were not attempted. The gelatin mass apparently acted as a matrix, for the capillaries and the fibroblasts extended into it from the adjacent mediastinum after eight days. Clotted fibrin was detected histologically in the interstices of the gelatin foam. A dense layer of clotted fibrin accumulated along the costal pleura forty-eight hours after pneumonectomy. Fibroblasts and capillaries extended eventually into the gelatin mass but this action was far less marked than from the mediastinum and the firm fibrous attachment of the gelatin to the costal pleura did not occur until much later.

Experimental observations indicate that the mediastinum is the site at which exudates largely appear and are removed from the pleural space. In this sense, therefore, the mediastinum serves the pleural space much as the omentum serves the peritoneal space.

NOCARDIOSIS: NOCARDIA ASTEROIDES INFECTION SIMULATING PULMONARY TUBERCULOSIS*

ROBERT P. GLOVER, WALLACE E. HERRELL, FORDYCE R. HEILMAN AND
EARL H. PFUETZE

Nocardiosis is not a new disease but it may likely be an unrecognized one. The infection is due to *Nocardia asteroides*, formerly called "*Actinomyces asteroides*." The clinician will do well to consider the presence of this disease in lesions simulating tuberculosis where bacteriologic confirmation of the diagnosis of tuberculosis is lacking. Before the era of modern chemotherapy, recovery from this infection was exceedingly rare. Of the thirty-six cases reported in the literature through 1940, only four (excluding a case of Madura foot cured by amputation) could be considered clear-cut examples of recovery. In all four cases the patients received sulfonamide therapy in one form or another in addition to other forms of treatment. We have reported a case of nocardiosis simulating pulmonary tuberculosis in which complete recovery appeared to have followed intensive therapy with sulfadiazine without surgical intervention. The antibiotics, penicillin and streptomycin, had failed to control the infection.

It would appear from the studies carried out in our laboratory as well as those carried out elsewhere that sulfadiazine is the drug of choice in the treatment of nocardiosis. The sensitivity of *Nocardia asteroides* to penicillin and streptomycin is not sufficiently great to suggest that these agents will control the infection unless, perhaps, they are combined with sulfonamide therapy.

It is suggested that the term "actinomycosis" be restricted to infection due to *Actinomyces bovis* and that "nocardiosis" be applied to infection due to *Nocardia asteroides*. It seems reasonable to conclude that patients suffering with this infection should recover if the condition is diagnosed early and is treated intensively with sulfadiazine.

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PULMONARY ABSCESS SECONDARY TO BLAND PULMONARY INFARCTION*

LOUIS LEVIN, JAMES W. KERNOHAN AND HERMAN J. MOERSCH

Findings in twenty-three cases of pulmonary abscess which developed after bland pulmonary infarction are presented and are analyzed.

While the diagnosis was definitely established clinically in only three cases, it is felt that abscess formation should be suspected in any case of infarction in which leukocytosis, unremitting fever and possibly a productive cough develop subsequently.

Pulmonary infarcts are especially prone to develop in cases of cardiac decompensation and, in any case of cardiac disease in which illness has been prolonged and unremitting fever has been present, the possibility of abscess formation should be considered.

A distinction should be made clinically between septic and aseptic embolic infarction. The term "infected infarct" should not be used unless the mode of infection is made clear.

In so far as the pathogenesis of these abscesses is concerned, it can be concluded that their development in a region of bland infarction depends upon the following factors:

1. The size of the region of infarction: the larger the region of infarction, the better the chances for abscess formation.
2. The state of blood supply to the region of infarction and the adequacy of collateral circulation.
3. The state of the surrounding pulmonary tissue, including such factors as coexistent congestion or atelectasis.
4. Bacteriologic factors, which include the presence or absence of dental, buccal and pharyngeal infections; the presence of bronchitis; the virulence of the organisms involved, and the massiveness of the infection.
5. The indeterminate, but apparently actively operating, factor of "tissue resistance" to the development of such abscesses in what, at first sight, appears to be a very fertile field for the growth of bacteria.

FUNCTIONAL RESPIRATORY DISTURBANCE WITH HYPER-VENTILATION AS A CAUSE OF SYMPTOMS†

C. E. MAYTUM

A large part of medical practice is concerned with the diagnosis and relief of symptoms caused by disturbance in function of normal organs rather than by organic disease. Functional disturbances of respiration are much more common than is ordinarily supposed and, in my experience, although the symptoms of such disturbances are rather characteristic they are more often unrecognized than are those of other functional dis-

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orders. The mechanism of their production is more easily explained to the patient than is that of other functional disorders and many or most of the symptoms can be reproduced at will by having the patient overbreathe. In addition, symptoms can usually be controlled promptly by very simple treatment.

I have arbitrarily divided the patients who have these symptoms into two groups according to their chief symptoms: (1) those whose chief symptom is "shortness of breath," and (2) those who have a variety of symptoms resulting from hyperventilation. In the second group, the respiratory symptoms may be overlooked not only by the patient but by the physician because the resulting symptoms may be severe and alarming.

The respiratory center is extremely complex and is influenced by many factors. While the respiratory center is automatic, it is to some extent under voluntary control; the rate and depth of respiration can be varied at will and breathing can be suspended for a minute or more. Pain and external stimulation by heat or cold can exert considerable influence on the rate and depth of respiration. The respiration also may be influenced by emotional disturbances such as fear, excitement or anger.

Sighing and yawning are probably the most common disturbances of respiratory rhythm. They occur normally in association with physical or nervous fatigue and, as a rule, are not disagreeable symptoms; however, certain persons who are anxious, worried or depressed and especially those who have an unstable nervous temperament may become unduly conscious of sighing (or yawning) and may have sensations and symptoms which are disagreeable and often actually alarming. If deep breathing or rapid breathing is continued for a time, hyperventilation and the symptoms of hyperventilation may appear and a vicious cycle of symptoms may develop. Hyperventilation occurs when either the depth or the rate of respiration is increased beyond that required to satisfy the oxygen requirements of the body. An excessive amount of carbon dioxide is lost (acapnia) and a change in the chemical balance of the body occurs. Because of the loss of carbon dioxide, there is a relative increase in the alkali reserve; alkalosis results and the symptoms of tetany may appear. This is a normal physiologic reaction and a few minutes of forced hyperventilation will produce symptoms in most normal persons. These symptoms disappear promptly when hyperventilation is stopped or when carbon dioxide is administered. Even severe tetany caused by hyperventilation can be stopped within a comparatively few minutes by the administration of carbon dioxide.

The chief complaint of patients in the first group is either "shortness of breath" or "attacks of shortness of breath." This is usually accompanied or precipitated by discomfort in the thorax, which is described as pain or a sense of constriction or weight in the chest. Cardiac palpitation is usually noted and there often is a feeling of weakness or dizziness which causes the patient to fear that he will lose consciousness. These sensations are very distressing to the patient, and the shortness of breath and the associated thoracic pain, palpitation and weakness or faintness may lead him to believe that serious heart disease is present. Symptoms may occur with exertion but they usually occur when the patient is at rest after exertion and when he is unusually tired. They may even awaken the patient from sleep, confused and fearful of suffocating. Persons who have relatively unstable

nervous systems are most commonly affected but under proper circumstances the disturbance may affect persons who are very stable. Attacks are more likely to occur when the patients are in a crowded place, such as a church, theater or department store, especially if the patients fear they may lose consciousness during an attack. The disturbance usually occurs intermittently or periodically although some patients are constantly aware of the feeling of inability to breathe properly, often for long periods. The patients usually complain of chronic fatigue and in some instances have refrained from work or have been kept in bed to avoid "further heart damage."

Actually, there is no real dyspnea and, when questioned, the patients describe their symptoms by one of the following phrases, which are very similar: "I can't catch my breath," "I can't get a full (or satisfactory) breath," "I can't get air into my lungs," "It won't go below a certain level" and, less often, "I have smothering spells." This similarity in describing the chief complaint is well illustrated by a comparison of two separate reports. In 1933, in reporting a case of tetany caused by hyperventilation, I called attention to a group of patients with functional breathing in these words: "An exaggerated form of sighing is seen in patients who have become respiration conscious, have a sense of tightness in the thorax and are unable to draw a satisfactory breath or to breathe below a certain level. Such patients are relieved of their distress by one or more long sighing breaths." Baker, in 1934, in discussing sighing as a symptom, said the patients complained of shortness of breath which on inquiry was found not to be true dyspnea but a curious disorder of breathing, variously described as "difficulty in taking a deep breath," "taking deep sighs," "inability to obtain a satisfactory breath" or even "stifling or suffocating turns."

With the exception of "smothering spells," these expressions are seldom used by patients who have true dyspnea and they are characteristic enough to suggest the diagnosis. If the patient's statement that "attacks of shortness of breath associated with pain in the chest, palpitation and weakness" is accepted without further questioning, an incorrect diagnosis is likely to be made. When the patient with functional shortness of breath is asked to describe in detail his sensations and symptoms, he will almost always use one or more of these phrases. In some cases, the patients will sigh frequently while the history is being taken. Regardless of the nature of the complaint, such sighing should suggest a functional basis for the symptoms. It is not unusual for the patient to call the physician's attention to his breathing, then take one or more unusually deep sighing breaths by using the accessory muscles of respiration and often pressing on his thorax to aid respiration. Finally, after a very deep breath, he will relax and call attention to the great difficulty he has had in getting his breath. Yawning during or preceding the attack is not uncommon and an occasional patient will say that he must yawn before he can get a satisfying breath. In some cases, relief is obtained by taking one or two deep breaths but in other cases the disturbance may last a long time. The patient may rush to a window or even out of doors in an effort to get more air, in spite of the fact that he is actually breathing much more air than he requires. This occurs much more often in functional than in organic dyspnea.

The symptoms of hyperventilation can be readily reproduced within a few minutes by voluntary forced breathing, and most persons will feel dizzy or lightheaded after they have taken only a few long breaths. If maximal inhalation with forced exhalation is carried on at a rate of thirty or more per minute, symptoms will appear very rapidly. With such extreme hyperventilation, dizziness, instability and a feeling of faintness will develop after the first few breaths. Within a minute or so, a sensation of tingling and numbness in the extremities will appear, and numbness and tingling of the face are not uncommon. The vision will become blurred and there will be a loss of sense of balance and an inability to think clearly. Even experimental subjects who are perfectly normal, at this stage, will experience a sense of excitement and apprehension which may be severe enough in some instances to make the individual discontinue the experiment. If forced breathing is continued, the muscles will become tense and co-ordination will be markedly decreased. Next the hands will become cramped and drawn into the position that is typical of carpopedal spasm. It is thought that some instances of "freezing to the stick" by airplane pilots are caused in this manner. Vasomotor symptoms such as pallor, perspiration and increased pulse rate will occur. At this point, even though he is overbreathing, an occasional person will feel a false sense of air hunger which is so marked that he is unable to voluntarily stop his deep breathing. In a few cases, partial or complete loss of consciousness will occur and the symptoms will closely resemble those of shock. All symptoms are promptly relieved by the administration of carbon dioxide.

Spontaneous hyperventilation associated with severe and alarming symptoms may develop rapidly at times when a patient who has become abnormally conscious of sighing feels that he cannot get his breath and, especially if he also feels faint, he is quite likely to attribute his symptoms to lack of air. He will then voluntarily increase his breathing in an attempt to obtain relief, whereupon more carbon dioxide is lost and his symptoms are aggravated.

Unless one is familiar with the symptoms of functional dyspnea and hyperventilation, the correct diagnosis is almost certain to be missed. A diagnosis of heart disease, pulmonary disease and even epilepsy may be made. This will increase the patient's apprehension and anxiety about his condition and will increase the nervous state which was responsible for the original symptoms. As a result, a state of semi-invalidism or chronic invalidism may develop. Sighing breathing is not a symptom of organic disease. When the patient is seen in an attack, the diagnosis is simple; when the patient is seen between attacks, the characteristic phrases which the patient uses to describe the attacks are easy to recognize. The presence of organic disease should be ruled out by careful examination and laboratory studies as indicated. One may occasionally find a fully compensated heart murmur in patients who have sighing breathing. If other evidences of cardiac disease are absent, one should remember White and Hahn's statement that the presence of sighing actually aids in evaluating the percentage of disability in a given case. Hyperventilation also may occur in patients with organic disease because of their anxiety and concern over their condition.

One should also consider hyperventilation in any case in which there is a

history of attacks of numbness or tingling of the extremities or face regardless of the associated symptoms. It also should be considered in any case in which a patient complains of attacks of weakness, palpitation and dizziness and pain in the thorax with or without paresthesia. It is surprising how often it is necessary to ask the patient specifically whether he has any trouble with his breathing, as it is often overlooked or not emphasized by the patient because of his concern over the secondary symptoms. If the patient is seen during an acute attack, the administration of carbon dioxide by rebreathing in a paper bag usually will relieve symptoms within a few minutes. When the presence of organic disease has been ruled out by examination, the symptoms can be reproduced by having the patient voluntarily overbreathe. This is not only a valuable diagnostic measure but an important part of therapy since it demonstrates to the patient that voluntary hyperventilation can cause the symptoms.

Treatment consists almost entirely of adequate explanation to the patient of the underlying mechanism of the disturbance. It should be emphasized that the abnormal breathing is a more or less normal reaction which may affect any person, particularly under conditions of fatigue or emotional stress. A brief explanation of the chemical changes which normally occur after hyperventilation and an explanation of the experimental production of tetany in normal persons, followed by voluntary overbreathing by the patient are usually all that are needed to avoid further attacks. Tetany can be relieved almost at once by holding the breath, or if the patient is unable to do this the tetany can be relieved by the administration of carbon dioxide or by rebreathing air. An attempt should be made to elicit, if possible, factors in the patient's life and environment which may account for his nervous and anxiety state. A careful and complete examination should be made in all cases. This should include roentgenographic examination of the thorax, electrocardiography and other laboratory studies as indicated, not only to reassure the patient but to rule out the presence of coexisting disease and to help prevent an error in diagnosis. Although symptoms tend to occur under the proper circumstances, in my experience a careful explanation of the condition and demonstration of its production result in almost complete relief.

AEROSOL THERAPY*

GILES A. KOELSCH

The introduction into the respiratory organs, by inhalation, of mists produced by nebulizing medicated solutions is known as aerosol therapy. The value of this type of therapy in diseases of the respiratory tract has come to be appreciated chiefly in the past three years.

The simplest type of apparatus for the production of aerosols from medicated solutions and that with which I have had the most experience

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is the Vaponefrin vaporizer.* The stream of air necessary to effect nebulization of the medicated solution is obtained from an oxygen tank. The tubing from the oxygen tank is connected to the base of a Y tube. Tubing from one arm of the Y is connected with the nebulizer. Tubing of similar length is connected to the other arm of the Y; the distal end of this tubing is left open. Four to six liters of oxygen per minute are allowed to flow through this apparatus. By covering the end of the open tube with his thumb, the patient can produce a medicated aerosol at will.

Diseases in which medicated aerosols have been used with benefit include bronchial asthma, sinusitis, bronchiectasis, bronchopneumonia, pulmonary abscess, acute laryngotracheobronchitis associated with edema, and severe pulmonary emphysema.

BRONCHIAL ASTHMA

A medicated aerosol first was used in bronchial asthma. As a means of affording the patient symptomatic relief, it is generally agreed that a 1:100 solution of epinephrine hydrochloride administered in this manner is most effective. By bringing this medicated aerosol into contact with the respiratory mucosa, quick absorption and prompt relief are insured in many instances. By having such an apparatus at his disposal, the patient is freed of the mental hazard occasioned by a delay in receiving an injection of epinephrine after an attack has started.

Administration of large doses of epinephrine by this method may produce untoward effects such as dryness of the pharyngeal mucosa, tachycardia, tremors and nausea. In order to prevent the occurrence of these effects, Hartman recommended the use of a 2 per cent solution of ethyl-nor-epinephrine [1-(3,4-dihydroxyphenyl)-2-amino-1-butanol] instead of a 1 per cent solution of epinephrine hydrochloride. He expressed the opinion that this preparation does not produce the untoward effects just mentioned and that it is just as effective as epinephrine in cases of uncomplicated intrinsic asthma but that epinephrine is definitely more effective than this preparation in cases in which the asthma is complicated by bronchial infection.

By employing the apparatus described earlier in this paper, either a 1 per cent solution of neosynephrin hydrochloride or a 1 per cent solution of epinephrine hydrochloride can be administered continuously. The unpleasant local effects on the pharyngeal mucosa which may be noticed after continuous therapy may be avoided if the medicament is placed in a 50 per cent solution of glycerin before nebulization is started. At the clinic, we have used a 0.25 per cent solution of neosynephrin hydrochloride in combination with penicillin for as long as two weeks without any evidence of unpleasant side effects. Whether or not we were able to obtain the bronchial dilatation desired, I believe is equivocal. Barach has stated that aerosol of neosynephrin hydrochloride is of value chiefly in cases in which the predominating disease is emphysema rather than bronchial asthma. He advises the patients to nebulize 1 c.c. of a 1 per cent solution of neosynephrin hydrochloride three to four times daily.

Because of its bronchodilating effect, aminophylline also is of great value

* This nebulizer may be obtained from the Vaponefrin Company, 328 South Jefferson street, Chicago 6, Illinois.

in the relief of asthma. Prigal reported the administration of aerosol of aminophylline to forty patients who had bronchial asthma. Ten to 20 c. c. of a solution containing 0.25 to 0.5 gm. of aminophylline was nebulized and inhaled continuously. Eighty per cent of the patients obtained some symptomatic relief, which was marked and of long duration in some cases but slight and temporary in others. After this treatment, an increase of from 7.1 to 56.9 per cent in the vital capacity was observed in nine cases. None of the symptoms commonly noted after the intravenous administration of aminophylline, such as nausea, vomiting and syncope, was observed after the administration of aminophylline aerosol.

In an effort to liquefy the tenacious sputum seen many times in bronchial asthma and to facilitate its expectoration, Prigal has suggested the use of an ammonium chloride aerosol alone or in combination with aminophylline aerosol. Theoretically, by bringing about bronchodilatation, aminophylline should augment the action of ammonium chloride. Prigal employed 10 c.c. of a 5 per cent solution of ammonium chloride for this purpose. This type of treatment can be given for a few days in preparation for the institution of treatment with penicillin aerosol.

It is logical that bactericidal agents should be given a trial in cases in which asthma may be due to bacterial infection, that is, in cases of so-called intrinsic asthma. Theoretically, intimate contact of the sulfonamide drugs with the infected respiratory mucosa, which can be achieved by aerosol therapy, should be desirable. Our experience with aerosols of the sulfonamide drugs is limited but the oral administration of these drugs in cases of chronic asthmatic bronchitis has not been followed by noticeable improvement unless the patients were suffering from an exacerbation of the asthma after an acute respiratory infection.

Applebaum administered an aerosol of sodium sulfathiazole in twelve cases of intrinsic bronchial asthma. He reported moderate to marked improvement in ten of the twelve cases. He also employed the same type of treatment in four cases of extrinsic bronchial asthma. Improvement was observed in only one of these cases; in this case, the improvement was said to be slight.

When penicillin became generally available for civilian practice, it was natural that it should be given a therapeutic trial in cases of asthmatic bronchitis. Investigators agree that administration of penicillin aerosol will produce a high concentration of penicillin at the site of infection in the bronchial walls and pulmonary parenchyma in cases of intrinsic bronchial asthma. In such cases, determinations of the concentration of penicillin in the blood and of the amount that is eliminated in the urine are of little value. Although such determinations furnish some indication of the amount of penicillin that is absorbed, they are not an indication of its effectiveness as a topical application. For administration, 30,000 to 50,000 units of the sodium or calcium salt of penicillin are dissolved in each cubic centimeter of physiologic solution of sodium chloride. Four to 5 c.c. of the resulting solution are administered daily with a nebulizer. The treatment may be continued for variable periods; seven to twenty-one days seem to be a reasonable trial period in the average case of intrinsic bronchial asthma. Unpleasant side effects are infrequent and are chiefly urticarial when they do appear. Administration of penicillin aerosol is preferable to the intra-

muscular administration of penicillin for the following reasons: (1) penicillin aerosol can be administered easily; (2) this type of administration is adaptable for use in the patient's home or in the physician's office; (3) it is relatively cheap, and (4) it is effective both locally and systemically.

Barach reported that either marked or significant moderate improvement occurred in a third of forty patients with asthma, to whom penicillin aerosol was administered. Vermilye obtained successful results with penicillin aerosol in twenty-five cases of intrinsic bronchial asthma. Prigal and his associates reported the results of treatment with penicillin aerosol in forty-nine cases of intrinsic bronchial asthma. They expressed the opinion that this type of therapy is of value only in those cases in which there is definite evidence of infection of the respiratory tract.

In cases of somewhat disabling chronic pulmonary disease, such as intrinsic bronchial asthma or bronchiectasis, acute exacerbations are likely to occur with respiratory infections. Prigal and his associates administered penicillin aerosol for three consecutive days following the first sign of a cold in twelve cases of this type. These investigators expressed the opinion that penicillin aerosol is of definite value in preventing serious trouble in such cases.

In contrast to these rather optimistic reports are those of other investigators. Engelsher treated seventy-four patients suffering from intractable intrinsic bronchial asthma by administering penicillin aerosol daily in adequate doses for periods of two to four weeks. He considered the results as strikingly disappointing and almost at complete variance with those of Vermilye. Segal treated twenty-two patients with intrinsic bronchial asthma with penicillin aerosol for periods ranging from three days to three weeks. Micro-organisms that were susceptible to penicillin disappeared promptly from the sputum but the results were generally disappointing from a clinical standpoint.

Olsen and I have administered penicillin aerosol in a number of cases of chronic intrinsic bronchial asthma. The daily volume of sputum was reduced in some instances and some patients stated that they could raise sputum with less effort. The degree of clinical improvement noted in some cases was not consistently greater than that which usually follows symptomatic treatment in the hospital with iodides, inhalations of oxygen and helium and the administration of aminophylline and bed rest. We feel that penicillin aerosol is worthy of further trial, especially in cases in which there is evidence that the asthma is severe because of the recent occurrence of an acute respiratory infection.

SINUSITIS

Sinusitis is another disease that has been reported to have been treated successfully with penicillin aerosol. It would seem from the reports in the literature that a further trial of this type of treatment of sinusitis is desirable. If penicillin aerosol can produce results as good as those reported in a considerable number of cases of sinusitis, and if it will make operation unnecessary, it certainly merits more widespread and continued use.

BRONCHIECTASIS

Bronchiectasis is a pulmonary disease in which penicillin aerosol has proved to be of great value. Not only does penicillin aerosol produce

clinical improvement in cases in which the disease is treated medically but it also reduces the incidence of serious postoperative complications in cases in which it is administered before operation.

Olsen reported the results of treatment by administration of penicillin aerosol alone or in combination with streptomycin in eighty-six cases of proved bronchiectasis. Forty-six of his patients were treated before pulmonary resection. No deaths occurred in the cases in which operation was performed and Olsen was convinced that such preparation does prevent serious postoperative complications.

The remaining forty patients, whose bronchiectasis was considered to be nonsurgical, were treated for periods ranging from two to eight weeks. Olsen expressed the opinion that no medical treatment will cure bronchiectasis but said that rest, good nutrition, favorable climate and regular postural drainage will help to control the bronchorrhea. Penicillin aerosol also has proved to be of great help in this respect. A striking reduction in the daily volume of sputum or complete relief of symptoms was noted in slightly more than 50 per cent of the forty cases. Olsen emphasized the importance of adequate bacteriologic studies of pulmonary secretions in all cases of pulmonary suppuration in which aerosol therapy is to be undertaken.

Levine reported the results which he obtained with penicillin aerosol in forty-two cases. In all of these cases there was definite bronchographic evidence of bronchiectasis and symptoms of bronchiectasis had been present for a long time. Improvement occurred in thirty-three cases. In nineteen of the thirty-three cases, all of the symptoms disappeared; in the remaining fourteen cases, the constitutional symptoms disappeared but the cough persisted. The good results that were obtained in these cases were attributable to direct topical application of the penicillin.

PNEUMONIA

Some authors have reported that the administration of penicillin aerosol produced good results in cases of bronchopneumonia. Although intramuscular administration of penicillin and the sulfonamide drugs is considered the preferred treatment in the average case of pneumonia, Segal expressed the opinion that penicillin aerosol is more effective than parenteral therapy in cases in which the pneumonia is due to streptococci, staphylococci or strains of *Klebsiella pneumoniae* that are sensitive to penicillin. In the treatment of pneumonia caused by staphylococci, he recommended that the administration of penicillin aerosol be continued for at least one week after all clinical and roentgenologic signs of the diseases have subsided, in order to prevent such complications as the formation of an abscess.

Segal recently reported twelve cases of pneumococcic pneumonia in which the administration of penicillin aerosol had produced complete recovery. Vermilye expressed the opinion that penicillin aerosol is of value in cases of pneumonitis. He administered 50,000 units of penicillin in the form of penicillin aerosol every three to four hours and also administered penicillin intramuscularly. He noted that pneumonia caused by staphylococci and *Hemophilus influenzae* may be resistant to penicillin but may respond to administration of the sulfonamide drugs.

PULMONARY ABSCESS

Administration of penicillin aerosol has produced variable results in cases of pulmonary abscess. Segal reported the results which he obtained by administering penicillin aerosol for from four to ten weeks in eleven cases of pulmonary abscess. In seven cases in which the abscess was aerobic, nonodoriferous and of the postpneumonic type, the patients recovered completely. The results were disappointing in the cases in which the abscess was of the atelectatic putrid type. Segal administered 50,000 units of penicillin in the form of an aerosol every three hours. This was supplemented by the intramuscular administration of 25,000 units of penicillin in cases in which the abscess was toxic and putrid. In one case in which the abscess was of the latter type, the patient was prepared for lobectomy with penicillin aerosol and made an uneventful recovery.

Olsen reported the results which he obtained with aerosols of antibiotics in four cases. A single abscess had been present for several months in two of these cases. An aerosol of penicillin and streptomycin was administered for four weeks. In one of the two cases, the abscess disappeared completely; in the other case, roentgenologic examination revealed that considerable improvement had occurred. The treatment did not produce any improvement in the two remaining cases.

LARYNGOTRACHEOBRONCHITIS

Aerosols are of real value in cases in which acute laryngotracheobronchitis is associated with edema. After tracheotomy has been performed, especially in cases in which the patients are children, Olsen has employed the nebulizer to moisten the oxygen which is administered. Distilled water or physiologic solution of sodium chloride alone or in combination with propylene glycol is nebulized by a stream of oxygen which is passed through the nebulizer into the tracheotomy tube. As a result of this treatment, no longer does the bronchoscopist have to maintain a constant vigil over the patients so as to be ready to remove the dry crusts which previously formed and constantly threatened to block the trachea or bronchi.

Segal administered penicillin aerosol and a gas mixture containing 75 per cent of helium and 25 per cent of oxygen in six cases in which acute laryngotracheobronchitis occurred as a complication of a severe infection. The aerosol may be directed into the tracheotomy opening. Although three of his patients appeared to be moribund when the treatment was instituted, dramatic improvement occurred in a short time. Segal expressed the opinion that the therapeutic results are most spectacular in this group of cases.

PULMONARY EMPHYSEMA

An attempt has been made to treat severe pulmonary emphysema with penicillin aerosol. In some instances, the vital capacity was slightly improved but the symptomatic relief which at times was noted was only temporary. It may be fairly stated that the results of aerosol therapy in cases of emphysema are not encouraging.

CONCLUSIONS

Aerosols of epinephrine are of value in relieving acute attacks of asthma. Aerosols of the antibiotics have proved of real value in combating the

infection associated with bronchiectasis and in preventing postoperative complications.

Aerosols of penicillin and neosynephrin have been of value in treating acute and chronic sinusitis.

Aerosols of penicillin and physiologic salt solution have been used successfully in the treatment of acute laryngotracheobronchitis associated with edema.

Aerosols of penicillin have been reported to be of value in the treatment of pneumonia and pulmonary abscess.

Aerosols of penicillin, ammonium chloride and aminophylline have been reported to be of value in enabling the patient with bronchial asthma to raise more easily the thick tenacious sputum encountered at times in this disease but no consistently favorable effect on the asthmatic attack itself has been noted.

Aerosols of penicillin or of the sulfonamide drugs may prove of value in relieving the asthmatic attack if it has followed an acute respiratory infection with fever. The specific effect in this instance is on the respiratory infection and not on the asthmatic attack *per se*.

INFLAMMATORY CARCINOMA OF THE BREAST*

ALFRED C. MEYER, MALCOLM B. DOCKERTY AND STUART W. HARRINGTON

Approximately 7,000 consecutive cases of malignant lesions of the breast encountered at the Mayo Clinic from 1933 through 1945 were reviewed. All cases in which inflammatory signs such as redness and edema were manifested or in which inflammatory disease had been diagnosed before the malignancy of the lesion was recognized were selected for further study. It became apparent that redness and edema were frequently present in cases of malignant lesion of the breast in which the breast was enlarged and in which the lesion was diffuse rather than localized. These cases were, therefore, added to the study. After discarding those cases in which the redness and edema were localized and obviously due to early necrosis and infection from invasion of the skin, seventy-four cases which seemed characteristic were finally selected. In sixty-one of these radical mastectomy had been performed, in two, simple mastectomy and in two, biopsy. Tissues obtained in these sixty-five cases were studied. For purposes of orientation and control fifty additional cases of noninflammatory carcinoma of the breast were subjected to a similar examination.

CLINICAL FINDINGS IN SEVENTY-FOUR CASES

Incidence.—Of approximately 7,000 cases of malignant lesion of the breast seventy-four were judged to be characteristic of the so-called inflammatory carcinoma type. This is an incidence of about 1 per cent.

Age and Sex.—The youngest patient in the series was thirty-two years

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old and the oldest was seventy-two. The average age was 52.6 years. All of the patients were women.

Side Affected.—It was interesting that the left breast was involved almost twice as frequently as the right. In the total of seventy-four cases the lesion affected the left breast primarily in forty-six; the right in twenty-eight.

Bilaterality.—At the time of initial examination at the clinic two patients already had bilateral inflammatory carcinoma and another had scirrhus carcinoma of different grade in the breast opposite the one which contained the inflammatory carcinoma. In six cases carcinoma subsequently developed in the remaining breast and one patient had undergone radical mastectomy for Paget's disease two years previous to her examination at the clinic.

Altogether ten patients or 13.5 per cent of the group eventually had bilateral carcinoma of the breast. The time interval between the appearance of disease in the first and second breasts varied from four months to seven years with an average of two years. In no instance did the carcinoma appear to occur simultaneously in both breasts.

Pregnancy and Lactation.—Twenty-four of the seventy-four patients had never been pregnant. One had been pregnant a short time before admission and was still lactating.

Duration of Symptoms.—The average duration of time before these patients came to the clinic after first noticing something wrong with their breasts was seven months. The longest period of time was five years and the shortest, eight days.

Signs and Symptoms.—As implied by the descriptive names previously given to this condition, its clinical signs are largely those of inflammation. So much did the condition in some of these breasts resemble an inflammatory process that it was erroneously and perhaps tragically treated as such. It is not surprising that in fourteen (18.9 per cent) of the seventy-four cases the condition was diagnosed inflammatory disease before its true carcinomatous nature was discovered.

The cardinal symptom of carcinoma of the breast is a lump, but in these cases a lump was noticed by only 62 per cent of the patients. Physical examination commonly revealed diffuse induration extending through much or all of the breast. In 45 per cent of the cases the tumor could not be palpated when the patient was examined at the clinic, and in the others it was poorly demarcated.

Most carcinomas do not cause an increase in the size of the breast. Inflammatory carcinoma, on the contrary, frequently enlarges the breast. Enlargement of one breast was the patient's first inkling of trouble in six cases (8.1 per cent). On examination at the clinic the affected breast was described as being enlarged grossly in thirty-eight cases, a little more than half the total number. The enlargement consisted not of a tumorous protrusion but rather of a symmetrical increase in the size of the whole breast.

The skin of the breasts was red or edematous or both, as if there was infection beneath. The redness varied from a rosy hue over the center or lower part to an angry red or violaceous color of the whole breast, sometimes even extending over the thoracic wall and to the axilla. Likewise the edema varied from slight puffiness of the skin to sodden thickening which pitted on pressure. Both the redness and edema were intensified when the patient

stood for a long time and receded when she lay down. The lower dependent portion of the breast was more often and more severely affected. Seventy-three per cent of the breasts were described as being red, and seventy-eight per cent were edematous on physical examination. (Since these data were taken from records which in some cases were incomplete it is felt that the incidence of redness and edema was probably higher, perhaps nearly 100 per cent.)

It is true that redness and edema occur over a carcinoma which is infiltrating the skin and causing necrosis and ulceration. These, however, result from true inflammation and are not to be confused with redness and edema caused by inflammatory carcinoma.

Pain was a frequent symptom. Fifty-three per cent of the patients had pain at some time during the course of their disease, and in twenty-six per cent of the cases pain was the first symptom.

Clinical examination revealed attachment of the skin to the underlying malignant tissue in forty-four cases (59.4 per cent).

The nipple was noted as being retracted in 54 per cent of the cases.

Despite extensive involvement of the breasts in many cases, there were only two instances of ulceration of the skin. It occurred very late in a case of bilateral massive involvement, which was treated only with roentgen rays. In the other case an ulcer of a deeply retracted nipple was present.

PATHOLOGIC FINDINGS IN SIXTY-FIVE CASES

Gross Examination.—The affected breasts were all large, and the discoloration and edema observed clinically were apparent in the specimens.

Skin.—On cut section the skin was found to be remarkably thickened and edematous, measuring from 2 mm. up to 8 mm. in thickness and averaging about 4 mm.

In none of the specimens was the skin destroyed by the growth. Even in those breasts in which the tumor seemed to occupy the entire substance of the breast the skin remained intact over it. In the two aforementioned exceptions pathologic examination could not be carried out in the case in which only irradiation was given and in the other the ulcer involved only the nipple.

Tumor.—In general the outstanding characteristics of the growth were its diffuseness and its extensiveness. In twenty-eight cases (43 per cent) the growth was so widespread that there was no evidence of localization whatsoever. Instead there were strands of diffusely growing carcinoma throughout the breast. Sometimes the clusters of malignant cells did not seem to be connected with one another, and in three such instances the clusters were so widely separated the growth was classified as multicentric. In sixteen specimens or 24.6 per cent there was a diffuse growth in the breasts, but a localized tumor could also be recognized. In nineteen cases or 29.2 per cent a localized tumor without diffuse extension was present.

When there was a localized tumor, in most instances it was very large. The size varied, however, from 2 by 1.5 by 1.5 cm. to 12 by 11 by 7 cm. The average size was 6 by 5 by 5 cm.

Among the growths which were well enough localized to allow specification of their positions in the breasts, seventeen occupied the center of the

breast; eight were so large as to occupy practically the entire breast; six were in the upper outer quadrant; and there was one each in the lower inner quadrant, upper half, lower half and outer half.

Lymph Nodes.—The axillary lymph nodes were enlarged and firm in all cases, but they did not differ in appearance from those of the usual case of carcinoma of the breast with gross metastasis to the axillary lymph nodes.

Microscopic Examination.—The massive involvement noted grossly was confirmed on microscopic examination. The carcinoma was widespread and was found to be growing in all directions from the main masses of tumor tissue. Especially prominent were the ligaments of Cooper in which the cancer apparently was spreading by way of the lymphatic vessels.

Lymphatics.—In the course of microscopic examination as the ligaments of Cooper were followed to the skin the subepidermal lymphatics were encountered spreading peripherally. In 80 per cent of the cases these lymphatics contained carcinoma cells, and this was a characteristic feature of the disease. These lymphatics lay at the level of the sweat and sebaceous glands and ran parallel to the surface of the skin. In some breasts every subepidermal lymphatic seemed plugged with cancer cells, while in others many sections had to be cut before involved lymphatics could be found. In thirteen breasts or 40 per cent carcinoma cells were not found in the subepidermal lymphatics, but in four of these and in the specimens removed for biopsy in the two cases in which the lesion was inoperable, carcinoma was found in the deeper lymphatics. Carcinoma cells were found in the lymphatics in 80 per cent of the cases in which surgical exploration was carried out. Axillary nodal metastasis was present in 100 per cent.

Blood Vessels.—The subepidermal capillaries, which run in the same plane as the lymphatics, were generally distended and engorged with blood. Cancer cells were found there in only two cases, but blood vessels containing carcinoma cells were found deeper in the breast in thirteen instances making a total of fifteen cases or 23 per cent in which intravascular spread occurred.

Skin.—The edema of the skin, visible grossly, was found on microscopic examination to be mostly in the dermis, through which ran the subepidermal lymphatic and blood vessels. The carcinoma cells were found in the lymphatics and blood vessels of the skin but did not infiltrate the skin directly. There were no cancer cells in the epidermis, nor was there necrosis or abscess formation.

Inflammation.—Lymphocytes and plasma cells were present in abundance at the margins of the carcinoma, but no more so than at the margins of the usual carcinoma of the breast. In the ligaments of Cooper and at the level of the subepidermal vessels there was an increased number of perivascular lymphocytes and plasma cells.

In twenty-eight cases (43 per cent) the increase was more marked than is usual in cases of carcinoma of the breast. It was impossible to correlate either the gross or microscopic extent of the disease with the number of lymphocytes and plasma cells. Breasts in which every subepidermal lymphatic seemed plugged with carcinoma did not necessarily display greater perivascular reaction than those breasts in which the presence of carcinoma cells was comparatively infrequent. Nor was the amount of redness and edema related to the number of lymphocytes and plasma cells present.

In no instance was there evidence of acute inflammation or suppuration.

Grade of Malignancy.—In all cases the carcinoma was highly anaplastic. Graded on the basis of 1 to 4 by Broders' method in which in grade 1 the cells are most differentiated and in grade 4, least differentiated, 88 per cent of the lesions were graded 4, and 12 per cent were graded 3. All were adenocarcinomas and five were muco producing.

Characteristics of Growth.—Nothing distinctive could be found in the individual cells nor in the architecture of the growth. It was, however, in the manner of its spread that this carcinoma manifested its individuality. Rather than growing as a directly infiltrating mass, it disseminated itself through lymphatics and blood vessels.

TREATMENT AND PROGNOSIS

Sixty-three of the seventy-four patients underwent mastectomy. In sixty-one cases radical mastectomy was performed and in two simple palliative mastectomy. All but one of the patients were given postoperative irradiation. In ten of the eleven cases in which the condition was inoperable because of obvious spread beyond the limits of surgical excision, roentgen therapy was given.

It was possible to follow up seven of the patients who had inoperable lesions. None of them lived more than three years. Of the group that received surgical treatment some were treated too recently for appraisal and it was not possible to follow up a few of the others. Some were known to have survived several years, and then further information concerning them could not be obtained.

There was no appreciable difference in prognosis in those cases in which the lesion was graded 3 and in those in which it was graded 4—an observation emphasizing the widespread nature of the disease.

Recognizable metastasis, aside from that to the axillary and supraclavicular nodes, was known to have developed in forty-two of the seventy-four cases studied. By far the most frequent site of metastasis was the skin (54 per cent of forty-one cases). In the twenty-three cases in which the lesion metastasized to the skin, it involved the skin of the thoracic wall in twenty cases, the arm and axilla on the same side in one case each and the abdominal wall on the side opposite the lesion in one case. In two instances there were recurrences in the scar left after previous mastectomy. Other common sites of metastasis were bone (38 per cent), thorax, including lung, pleura and mediastinum (33 per cent) and the opposite breast (21 per cent). The total of the percentages equals more than 100 per cent since in several cases there was more than one site of metastasis.

COMMENT

The age incidence for inflammatory carcinoma in our series seemed to be about that for carcinoma of the breast in general.

Among the seventy-four cases studied pregnancy and lactation did not appear to have any relationship to the development of inflammatory carcinoma.

It is quite likely that stasis also accounts for the redness and discoloration of the breast. Like the edema, the redness tends to disappear when the patient is lying down. Extensive cancer plus inadequate lymphatic drainage due to the blockage of lymphatics by carcinoma produces increased pressure

within the breast and the resultant passive hyperemia. The presence of an increased amount of blood, especially in the subepidermal region, leads to redness and blueness of the skin. When the patient is in the recumbent position the effect of gravity somewhat reduces the amount of stasis and modifies the circulatory findings.

In no instance was there either clinical or pathologic evidence of infection to account for the inflammatory signs in our series of cases. At microscopic examination lymphocytes and plasma cells were often found in the vicinity of the cancer, but no more than in comparable carcinomas without clinical signs of inflammation. Clumps of lymphocytes were also found in the subepidermal tissue as previously described by Learmonth, Ewing (according to Lee and Tannenbaum) and Leitch. The finding of these clumps may indicate that stasis of lymph or possibly a reaction to some irritant product of the carcinoma had occurred.

All observers who have studied inflammatory carcinoma have been impressed with its poor prognosis. In our series surgical treatment was employed in all cases in which the lesion had not obviously spread beyond the limits of excision. The fact that three patients survived for five years after operation would seem to justify this type of therapy.

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BRAIN, SPINAL CORD AND NERVES

BRAIN TUMORS; VALUE OF EARLY DIAGNOSIS*

ALFRED W. ADSON

In diagnosis of an organic intracranial lesion, it is extremely important to proceed in an orderly manner by taking the history carefully and by conducting physical, neurologic, ophthalmologic, roentgenographic and selected laboratory examinations. It is impracticable to rely on special measures, such as pneumoventriculography or pneumo-encephalography, to the exclusion of evidence elicited in the course of the routine examination.

A thoroughly taken history is invaluable when working out a differential diagnosis. General examination further assists in distinguishing between coexisting diseases; neurologic examination discloses mental states, normal or abnormal reflexes and motor and sensory findings. Ophthalmologic examination reveals the condition of ocular movements, the presence or absence of pathologic conditions of the ocular fundi and visual fields, such as ocular palsy, papilledema, optic neuritis, optic atrophy and defects in the perimetric fields. These data aid in confirmation of the impressions obtained at neurologic examination. On roentgenographic examination, which includes making ordinary and stereoscopic roentgenograms, evidence of erosion, convolutional markings, hyperostosis, inflammatory lesions of the skull and deposits of calcium in neoplasms and vascular lesions can be found.

Pneumo-encephalography is of value in showing the evidence of convolutional destruction and cerebral atrophy in traumatic and circulatory disease, and ventricular deformities in circulatory, neoplastic and congenital lesions, but it may be a dangerous procedure if a cerebral neoplasm is present. Pneumoventriculography has become used widely and is valuable in the localization of tumors early in their growth and in silent areas. Occasionally it is used preliminary to operation to estimate the size and depth of localized tumors.

Electro-encephalography is one of the newer procedures employed in the localization of cerebral lesions. The purpose of making an electro-encephalogram is to determine if the normal brain waves have been disturbed by a neoplasm. Present knowledge of electro-encephalography makes it a reasonable aid in the differential diagnosis; however, it is not infallible.

The choice of laboratory tests depends on the history of coexisting diseases and the physical and neurologic findings. Spinal puncture and examination of spinal fluid are indicated if trauma has occurred and circulatory and inflammatory lesions are present, but only occasionally if cerebral neoplasms are present. These procedures reveal the presence or absence of

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blood, intraspinal pressure and the presence or absence of organisms and furnish valuable information concerning changes in protein content, other chemical changes in the fluid, and the number and morphology of the cells. In cases in which the presence of syphilis and parasitic lesions is suspected, the serologic test of the spinal fluid offers material assistance in arriving at a diagnosis. Spinal puncture is contraindicated in the presence of increased intracranial pressure when papilledema is of more than 2 diopters.

SYMPTOMS OF INCREASED INTRACRANIAL PRESSURE

The early signs of increased intracranial pressure are headache, vomiting and choked disks. It is not necessary for all three to develop simultaneously, but sooner or later they all will be present. Symptoms of pressure due to tumors situated in the region of the optic chiasm, in the corticospinal and motor areas, and in the cerebellopontine angle are the exception since symptoms of localization develop before those of increased intracranial pressure.

If the patient is ambulatory, headache occurs daily in the early morning hours and frequently awakens the patient about 4 a.m. Vomiting is of the projectile type and is often associated with headache and with movements of the head. Pain in the occiput associated with rigidity of the neck are accompanying symptoms of infratentorial tumors. Papilledema, or choked disks, may be confused with edema of retrobulbar neuritis, but when associated with headache and vomiting increased intracranial pressure is invariably present. However, tumors situated in the sella turcica or in the chiasmal region which produce direct pressure on the optic nerves will cause pallor of the optic disks instead of edema. When they grow to sufficient size to obstruct the free flow of cerebrospinal fluid in the ventricles and subarachnoid spaces, edema of the disks will be followed later by secondary optic atrophy. Lesions that obstruct the third and fourth ventricles produce a high degree of, and rapidly progressing, choked disks.

SYMPTOMS OF LOCALIZATION

The syndromes of tumor vary considerably according to position, rate of growth, size and pathologic features. Each group produces a chain of symptoms peculiar to its own life cycle. It is apparent that lesions of the frontal lobes will give rise to psychic and personality changes. Those arising in the speech and motor centers will produce aphasia, apraxia, jacksonian convulsions, convulsions of the grand mal type, monoplegia and hemiplegia. Other symptoms develop as respective centers, nuclei and tracts become invaded or destroyed or deprived of their normal blood supply by indirect pressure.

In considering the differential diagnosis it must be borne in mind that certain features in the symptoms resulting from cerebral trauma, inflammatory diseases and suppurative diseases may resemble those of tumor. Therefore, it is important to obtain a thorough chronologic history to elicit differential diagnostic facts. The symptoms of cerebral arteriosclerosis rarely are confused with those resulting from tumor, since evidence of increased intracranial pressure is lacking. Occasionally cerebral thrombosis of slow progression, subdural hemorrhage and intracerebral hemorrhage may

readily produce symptoms simulating tumor, and require surgical intervention in order that proper surgical treatment may be administered in cases of frank hemorrhage and that an operable tumor may not be overlooked.

SURGICAL CONSIDERATION

Surgically brain tumors are placed in two large groups; one includes the encapsulated and accessible infiltrating tumors and the other includes the diffuse, infiltrating and inaccessible tumors. It is apparent that the encapsulated accessible tumor lends itself best to surgical removal; however, the infiltrating tumor, when situated in a silent area, also can be removed by removing tissue about the tumor. More often than not, in the group of non-encapsulated tumors, the surgeon is compelled to perform subtotal resection, removing necrotic, cystic material with mural nodules and tumor masses from within the tumor in order to avoid increasing the existing paralysis. Radical resections of diffuse infiltrating tumors are avoided if their removal may cause hemiplegia. I prefer to secure a shorter period of relief and preservation of more normal function than an extended, indefinite period of relief and spastic hemiplegia. Decompression should never be substituted for removal of tumor when it is at all possible to perform radical operation, but decompression does serve as an auxiliary measure in subtotal resection of tumors and serves as a measure of temporary relief in the treatment of many inoperable tumors.

Inoperable tumors developing in or involving the corpus callosum, basal nuclei, brain stem, pons and medulla present difficult surgical problems, since their removal is impossible and little, if any, relief is accomplished with decompression. Many of these tumors are of the variety known as medulloblastoma and spongioblastoma multiforme. Radiotherapy offers temporary relief. Treatment with high-voltage roentgen rays constitutes the most suitable type of therapy for adults who will co-operate, since it can be administered in massive doses in a short period. Radium is most suitable in treatment of similar lesions of children or un-co-operative patients, since the blocks of radium can be bandaged on the heads of patients. It always should be remembered that radiotherapy may increase symptoms for the first ten days due to swelling and edema of tumor cells. Treatment of these symptoms may require dehydration, which can be accomplished by limitation of intake of fluids and administration of diuretics and saline cathartics.

INTRACRANIAL HEMATOMAS*

WINCHELL McK. CRAIG

Intracranial hematomas are usually differentiated from acute intracranial hemorrhages by the fact that they become manifest after a delay subsequent to head injury and that they simulate brain tumors in many of their aspects. The most common of the intracranial hematomas is the

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chronic subdural hematoma. Somewhat rarer in occurrence are the intracerebral hematomas which may resemble the subdural hematomas, as well as tumors, abscesses or degenerative lesions, in symptomatology.

CHRONIC SUBDURAL HEMATOMA

Chronic subdural hematomas which may occur after mild intracranial injuries require operative removal and they should be diagnosed fairly early to prevent irreparable damage to the underlying brain. Chronic subdural hematoma has been confused with hemorrhagic pachymeningitis; in the minds of some surgeons and pathologists there is a question as to whether hemorrhagic pachymeningitis is the result of infection and causes the accident or whether the chronic subdural hematoma develops after the accident, from a tear in the small veins associated with the longitudinal sinus or from a tear in the sinus itself. Putnam and Cushing expressed the opinion that there were two types of hemorrhagic subdural hematoma: (1) the vascular type which is seen frequently at necropsy after death from chronic alcoholism and chronic wasting disease and (2) the reactive or traumatic type. In recent years some neurologic surgeons have come to look upon chronic subdural hematoma as being relatively frequent after mild head injuries. Subdural hematoma may occur at any age and may affect either sex, but it seems to be more frequent among men because of their greater exposure to injury. Subdural hematoma should be suspected in any case in which symptoms of increased intracranial pressure or intracranial difficulties develop a few days to months after an injury to the head. The usual points in the history are headache, vomiting, gradual diminution in visual acuity, diplopia, convulsions and mental disturbances. No one factor is common in all cases, and in spite of the fact that localization of the hematoma is fairly constant over the convex portion of the cerebral hemisphere, the findings on neurologic examination are extremely variable and are frequently so confusing that in order to make the diagnosis it is necessary to resort to ventriculography.

The fact that subdural hematoma occurs after trivial injuries to the head brings up the question of the mechanism of the development of the blood clot. Most of the investigators have concluded that the source of hemorrhage almost always is one of the branching veins running from the cerebral cortex across the subdural space into the superior longitudinal sinus. Once the clot has formed, the latent period is rather difficult to explain. Zollinger and Gross explained that liquefaction probably takes place within the clot, and that the wall of the sac acts as a semipermeable membrane. They further stated that the fluid contents of the sac, which have a higher osmotic pressure than does cerebrospinal fluid, increase in volume as a result of osmosis, thus gradually distending the sac. This explanation has been questioned, but up to the present time it seems to be the most satisfactory one.

The treatment of chronic subdural hematoma is entirely surgical, and osteoplastic flaps formerly were reflected in all cases. Fleming and Jones suggested double trephine openings, one placed posteriorly, and one anteriorly, for the purpose of aspirating and washing out the contents of the sac. McKenzie has recommended the removal of the contents of the sac by suction through a small opening in the bone and subsequent drainage

of the subdural space for forty-eight hours. Just as is the case in so many surgical conditions, no single procedure is applicable in all cases, and while the aspiration of the contents may be tried through one or two openings, an osteoplastic flap should be reflected in those cases in which the clot is still partly solidified and extends beneath the temporal lobe. On one or two occasions, subdural hematomas which apparently had been removed through one or two trephine openings were exposed through an osteoplastic flap, and the residue of the clot was found to be causing residual symptoms. After the entire clot had been removed, an uneventful convalescence followed.

It is true that some trivial injuries to the head are followed by symptoms which simulate those of chronic subdural hematoma but which respond to more conservative treatment. Mild injuries to the head, such as in the case of a girl who fell from a tree, may be followed by drowsiness or generalized convulsions which, upon spinal puncture, seem to be relieved. Spinal punctures, of course, should be done in these cases only when increased intracranial pressure is not present as evidenced by papilledema. In these cases in which there is no choking of the disk, spinal puncture can be done safely, and if the procedure reveals yellow cerebrospinal fluid, then one is impressed with the fact that there must have been some small hemorrhage which can be relieved by repeated spinal punctures. There always has been some controversy over the place of spinal puncture in the diagnosis and treatment of acute head injury, but in the chronic or delayed conditions, the safety of the procedure is almost assured. In the presence of papilledema or choked disks, spinal puncture is definitely contraindicated.

Chronic subdural hematoma may occur at any age, and if it affects infants, the damage to the brain is sometimes extensive and permanent. However much one should be aware of the presence of chronic subdural hematomas in infants, one should also be aware of the fact that hemorrhagic pachymeningitis is also frequent. In all cases of infants with suspected chronic subdural hematoma, provided the fontanels are open, aspiration should be done and probably ventriculograms should be made. In spite of the fact that there is definite evidence of chronic subdural hematoma, the lesions of a definite hemorrhagic pachymeningitis may completely cover the entire brain.

Neurologic surgeons are constantly being reminded that chronic subdural hematoma may be bilateral and that such occurrence should be suspected in all cases in which a subdural hematoma is found on one side.

Slight injuries to the head which are almost too trivial to be mentioned may be the cause of hematomas. Frequently, when no mention of an injury to the head has been made in the preoperative history, the patient can recall such accidents only with difficulty.

Intracranial hematomas of the subdural type may be caused by mild or severe head injuries, and quite frequently they occur in unsuspected cases. A few years ago all of the cases of chronic subdural hematoma encountered at the clinic were reviewed, and it was surprising to find in how many of them it was impossible to obtain a history of cranial injury. Chronic subdural hematoma usually follows a slight injury.

In considering the pathologic changes, the question of whether chronic subdural hematoma is an ordinary blood clot is often raised. It is difficult to

explain how a man may sustain a blow on the head and be perfectly well for six, eight or ten weeks thereafter, before symptoms of intracranial injury appear. At operation, an organized, liquefying blood clot is found beneath the dura, and the dura can be stripped off a definite capsule. The clot is increased in a capsule of fibroblastic tissue which feels like a rubber sac. The contents of the sac consist of fluid which has the color and consistency of bile. Another interesting thing is that when the clot is solid, it is laminated, as if small hemorrhages had occurred at intervals. The supposition is that the hemorrhage is of venous origin; that a small vessel in the longitudinal sinus is torn; and that the bleeding is encouraged every time the intracranial pressure is changed. It is common knowledge that during craniotomy, bulging of the brain can be seen if the patient grunts or coughs while he is anesthetized, and if any other strain causes increase in the intracranial pressure. After an injury to the head, a small hemorrhage probably occurs which increases with changes in intracranial pressure until it has become fairly large. The clot becomes organized, endothelial cells form a capsule around this clot and liquefaction then takes place. This sac of fluid lies in the subarachnoid space and is in contact with the cerebrospinal fluid. It is believed that the osmotic pressure causes absorption of the cerebrospinal fluid, with the result that the sac enlarges. This explains the latent period and it explains why the symptoms of chronic subdural hematoma simulate those of tumor of the brain. Intracranial pressure is increased, as is evidenced by headache, vomiting, choked disks and localizing signs, such as weakness of one or more extremities, nystagmus and ataxia. If operation is performed early, it usually is followed by immediate relief of symptoms.

INTRACEREBRAL HEMATOMAS

In addition to chronic subdural hematoma, there is also an intracerebral type of hematoma which is within the brain substance itself and which has been looked upon as a result of spontaneous, intracerebral hemorrhage. Spontaneous, intracerebral hemorrhage is a rather rare condition but it has occurred frequently enough to be of importance in the differential diagnosis of tumor of the brain. In the cases at the clinic in which the patients responded to operation, the hemorrhage has always been situated in the cerebral hemisphere, not in the brain stem or in the cerebellum, and has followed injury, strenuous exercise, severe emotional strain, or in one instance, endocarditis.

In discussing the surgical treatment of the intracerebral hematoma, one is impressed, from the review of the literature, with the fact that intracerebral hemorrhage was reported fairly frequently but that only a few references to the successful surgical treatment of such a hemorrhage were found. Numerous authors have called attention to the fact that craniotomy with evacuation of the clot had been suggested, but Cushing was probably one of the earliest surgeons actually to carry out this procedure. He reported a case of spontaneous intracerebral hemorrhage in which craniotomy was performed and the clot was removed, with relief of intracranial hypertension and hemiplegia. In this case a man aged forty years evidently suffered from apoplexy as he fell from a bicycle. He was taken to a hospital in a state of unconsciousness and thirty-six hours later, at which time a right

hemiplegia had developed, he was operated upon and a hematoma 1 cm. deep was evacuated. He recovered from this operation but died two weeks later of pneumonia.

With regard to the etiology of spontaneous intracerebral hemorrhage, in a review of nine cases it is interesting to note that in two cases hemorrhage was definitely the result of trauma. In the third case the symptoms occurred two weeks after the patient had attended a convention; while there was no definite history of trauma, there was a period of strenuous exertion and excitement. In the fourth case the hemorrhage was associated with rheumatic heart disease and endocarditis due to *Streptococcus viridans*, suggesting a bacteriologic origin. In the fifth case the cause was uncertain, as the patient was found unconscious after he had fallen from a farm wagon, and it was difficult to determine whether or not the unconsciousness preceded the fall. In the sixth and seventh cases, in one of which the patient was a woman, in the other a man, hemorrhage evidently occurred spontaneously while the patients were under emotional stress; there were no other etiologic factors. In the eighth case hemorrhage occurred suddenly without apparent cause, and in the ninth case it was associated with a metastatic melanoma. In all these cases after the clot had been evacuated and the cavity explored at operation, there were no active bleeding points; in one case a pseudo-membrane surrounded the hemorrhage, and it was removed. This would seem to disprove the theory that the bleeding was of arterial origin; it was thought that the spontaneous intracerebral hemorrhage was of venous origin.

Patients who have suffered from spontaneous intracerebral hemorrhage can be relieved by operation. Trauma, strenuous exercise, emotional strain, endocarditis and metastatic melanomas have been found to be contributing factors.

The etiologic factors in most of the cases of intracerebral hematoma are rather indefinite. The condition may be due to faulty musculature of the arterioles or venules within the brain substance, and hemorrhage may result from rupture of a small sacculation. Since the hemorrhage does not result in extensive extravasation, there is an inclination at the clinic to believe that the rupture in the vascular system occurs on the venous side. In two of the cases referred to herein there was a definite lamination about the clot, and a fresh clot had formed in the dependent portion of the original clot as if recurrent hemorrhages had taken place.

The symptoms in most instances of this type of case developed rather suddenly after injury, violent exercise or emotional strain. In most cases the hemorrhage was accompanied by an attack of unconsciousness and by progressive paralysis. The progression of symptoms became more or less stationary within a short time, but while the progression seemed to cease, signs of increased intracranial pressure developed. In some instances paralysis was slowly progressive, and the symptoms therefore resembled those that developed as a result of an intracranial neoplasm.

In summary, it is apparent that intracranial hematomas may develop spontaneously or after an injury, and from the standpoint of diagnosis they very seldom can be distinguished from intracranial tumor.

It is an impressive fact that in the diagnosis of intracranial lesions, of whatever type or origin, a complete examination is necessary, including

the examination of the fields and fundi of the eyes, the roentgenologic examination of the head, a general examination to rule out systemic disease and a complete neurologic examination to bring out any change in motion or sensation. Frequently it is also necessary to make electro-encephalograms, as well as encephalograms made with the aid of injected air to determine the location of the lesion. At operation usually a bluish discoloration of the dura is indicative of a chronic subdural hematoma. Similarly, a bluish discoloration of the cortex may indicate a subcortical hemorrhage. However, frequently at operation a *broadening and flattening of the convolution* is the only sign indicative of a subcortical lesion, and it is only when the lesion is explored with a large needle that an intracerebral hematoma is encountered, as indicated by the aspiration of old blood or yellow bloody fluid. So, from the standpoint of diagnosis, it is frequently difficult to distinguish intracranial hematoma from an expanding lesion of the brain, including the different types of intracranial neoplasms.

Finally, it might be said that frequently head injuries are associated with tumors and that the history of injury may be misleading in cases in which a diagnosis of intracerebral hematoma is suspected. At the clinic cases of intracerebral tumors have been seen in which there were no evident signs or symptoms until a head injury was sustained, but any intracranial injury may be followed by subdural hematoma or intracerebral hemorrhage.

One should never rely upon the history as the basis for determining the nature of an intracranial lesion. There is a definite saying among neurologic surgeons that every intracranial lesion should be explored in order to determine the nature of the underlying pathology because frequently there is found a subdural hematoma, an intracerebral hematoma or a benign tumor which responds satisfactorily to operation. Thus it is felt that even in the presence of a definite intracranial hematoma, operation is the treatment of choice, and until such a hematoma is completely evacuated, the treatment has not been completed.

THE USE OF POLYTHENE FILM AS A DURAL SUBSTITUTE: AN EXPERIMENTAL AND CLINICAL STUDY*

M. HUNTER BROWN, JOHN H. GRINDLAY AND WINCHELL McK. CRAIG

An experimental study of polythene film has shown that it fulfills the criteria of a dural substitute.

Polythene film does not adhere to the underlying leptomeninges and cerebral cortex. This property permits the dura to regenerate between the film and the arachnoid. Histologic studies indicate that there is no reaction in the pia-arachnoid and cortex to the presence of the film.

A clinical trial of polythene film has shown that it is a satisfactory dural substitute and suggests other important uses of polythene in neurologic surgery (tabulation).

* Abstract of paper published in full in *Surgery, Gynecology and Obstetrics*, 86:663-668 (June) 1948.

TABULATION

CLINICAL APPLICATIONS OF POLYTHENE FILM

1. Replacement of dura.
 - a. Meningioma.
 - b. Fibrosarcoma.
 - c. Other tumors invading dura.
2. Repair of dura.
 - a. Cerebrospinal rhinorrhea.
 - b. Other spinal fluid fistulas.
 - c. Meningocele.
3. Prevention of meningocerebral cicatrix.
 - a. Penetrating craniocerebral wounds.
 - b. Lobotomy.
4. Decompression—cerebral and cerebellar.
5. Peripheral nerve anastomosis.
 - a. Tubularization.
 - b. Protection of nerve ends in two-stage operation.
6. Prevention of arterial intimal damage.
 - a. Ligation for intracranial aneurysm.
7. Cosmetic.
 - a. Burr hole covering.
8. Control of hemorrhage by tamponade.

GLIOMAS OF THE CEREBELLOPONTINE ANGLE*

JAMES W. KERNOHAN, HENRY W. WOLTMAN AND ALFRED W. ADSON

The histories and findings in ten cases of tumor of the brain are reported in the complete paper because they present some unusual features. All the tumors were extramedullary gliomas situated in the cerebellopontine angle. They seem to arise in the lateral recess from a lamina of glial tissue that can be demonstrated in normal brains. This plate of tissue arises from the floor of the lateral recess, whence it passes laterally and posteriorly until it approaches the seventh and eighth nerve roots. There it extends laterally along the course of the nerves for a short distance. This plate of tissue has an ependymal lining on its upper and lateral surface and there are collections of ependymal cells, as small irregular groups or as canals, embedded in glial tissue which is made up mostly of astrocytes. Occasional nerve cells are present. These tumors may surround local nerves and vessels and may compress but do not invade the cerebellum, pons or medulla. Eight of these tumors were ependymomas; two were astrocytomas.

The salient clinical features were as follows: Seven patients were female and three male. Seven were children and three adults. In eight cases the duration of the illness was one year or less, in one it was a year and a half and in one it was unknown. Vomiting and headache were the presenting symptoms in most cases, a visual disturbance and ataxia in about a half and unilateral deafness in two.

* Abstract of paper published in full in the *Journal of Neuropathology and Experimental Neurology*. (In press.)

Seven patients had abducens palsy; six had ataxia; five had choked disks, nystagmus, seventh nerve palsy, rigid neck and pyramidal signs; four had an absent corneal reflex, unilateral deafness and absent tendon reflexes, and one had dysphagia.

The diagnosis of tumor was made in seven cases and suspected in one more, that of encephalitis in one and that of subarachnoid hemorrhage in a case in which hypertension was present, a complication that led us astray.

The eight patients with ependymomas died; the two with astrocytomas were alive when they were heard from last. It should be noted, however, that there may have been other patients with extramedullary gliomas who may have survived. However, none of these were included in this series since we could not be certain of the extramedullary origin of the tumor.

EXTENSIVE SYMMETRICAL CEREBRAL CALCIFICATION AND CHORIORETINITIS IN IDENTICAL TWINS (TOXOPLASMOSIS?); CLINICAL REPORT OF CASES*

KENNETH H. ABBOTT AND JOHN D. CAMP

Eleven year old identical twin boys were studied clinically because of visual disturbances and of disturbances of movement in the right extremities. The disturbances were more evident in the more severely affected of the two boys, who also had bilaterally symmetrical, extensive, dense calcification in the cerebrum with minor involvement of the cerebellum. Both patients had extensive chorioretinitis, which was more severe unilaterally, associated with retinal angiomas. Blood serum from each of the twins neutralized *Toxoplasma* organisms.

The pathogenesis and the histopathology of this syndrome, symmetrical cerebral calcification, chorioretinitis with retinal angiomas and toxoplasmosis, are unknown. Although a degenerative process occurring in symmetrical anomalies of vascular or heterotopic nervous tissue or both may be the causal factor, it would seem more plausible that the syndrome is due to inflammation, probably consequent to chronic toxoplasmosis.

* Abstract of paper published in full in the Bulletin of the Los Angeles Neurological Society, 12:38-47 (Mar.) 1947.

THE ELECTRO-ENCEPHALOGRAM IN TUMORS
OF THE POSTERIOR FOSSA*REGINALD G. BICKFORD AND EDWARD J. BALDES
(INTRODUCED BY GRACE M. ROTH)

The electro-encephalographic findings in a group of fifty predominantly adult persons who had tumors of the posterior fossa can be classified as follows: (1) normal records in 6 per cent of cases; (2) paroxysmal rhythms with frequencies of 3 to 7 and 18 to 22 cycles per second, with a tendency to repetitive wave forms and synchronous activity from all parts of the head in 56 per cent and (3) a less uniform group showing continuous delta rhythms with a frequency of 2 to 6 cycles per second and delta foci unrelated to the site of the tumor in 38 per cent of cases.

Many of the characteristic abnormalities were seen to advantage in transverse leads from homologous parts of the scalp. For instance, in 63 per cent of all records abnormal waves were noted in the inter-ear lead.

The alpha rhythm showed a marked instability of frequency (in excess of 2 cycles per second) in 42 per cent of the whole group, whereas in another 14 per cent the alpha rhythm was completely disorganized by delta waves. A fast activity with a frequency between 18 and 22 cycles per second either continuous, or in episodes, was present in 20 per cent of records. A further characteristic feature was the inhibition of abnormal activity when the patients opened their eyes. This occurred in 60 per cent of cases.

The group of records which showed paroxysmal rhythms is interesting since the majority of tracings were indistinguishable from those seen in cases of epilepsy; even the classical wave forms were reproduced. These rhythms, however, cannot represent true epileptic activity since clinical epilepsy from these tumors is almost unknown.

The resemblance might be explained on the basis of a common diencephalic origin for the rhythms of epilepsy and those associated with tumors of the posterior fossa. In the latter case, expansion of the third ventricle which is known to be an early event in the progress of tumors of the posterior fossa presumably would initiate the diencephalic disturbance.

From the diagnostic point of view, it is suggested that the occurrence of a rhythm typical of epilepsy in the tracing from a patient without previous or family history of epilepsy should arouse a suspicion of tumor of the posterior fossa.

* From the Proceedings of the Central Society for Clinical Research, 20:87-88, 1947, *Journal of Laboratory and Clinical Medicine*, 32:1319-1328 (Dec.) 1947.

TUMORS OF THE SPINAL CORD*

WINCHELL McK CRAIG

Intraspinal tumors as a cause of pain and disability have been overlooked in recent years because of the discovery that many of the heretofore unexplained pains in the back and upper and lower extremities actually are the results of protruded intervertebral disks.

Clinically, the majority of intraspinal tumors are benign and can be removed. The possibility of metastatic lesions must be kept in mind, but the age of the patient and a careful general examination will rule this out. Degenerative lesions of the spinal cord also must be ruled out before a definite diagnosis can be made. Careful neurologic examination, including attention to both sensory and motor areas, should be carried out in all cases. Roentgenologic examination of the vertebral column often is of value in differential diagnosis. The introduction of iodized oil within the subarachnoid space has been of immense value in the localization of intraspinal tumors before they have progressed to the point of compression at which definite sensory levels are produced.

Intraspinal operations can be carried out with a minimum of danger. The majority of intraspinal tumors are benign and removable.

Anatomically, intraspinal tumors can be classed as extradural, intradural and intramedullary. Fortunately, the majority of tumors occur outside of the spinal cord, and the symptoms are produced by pressure. Surgical removal of this compression of the spinal cord results in relief of the clinical symptoms. The cardinal symptom of intraspinal tumors is pain—pain which appears intermittently and is increased by coughing and sneezing, pain which occurs after the patient is lying in the prone position, pain which usually causes the patient to arise early in the morning and sit in a chair, and which as a rule is confined to certain dermatomes, indicating the compression of one or more spinal nerves. Compression of the spinal cord produces symptoms, both sensory and motor; generally the so-called Brown-Séquard syndrome is present, with motor symptoms on the ipsilateral side and sensory symptoms on the contralateral side.

It is sometimes difficult to distinguish intramedullary tumors of the spinal cord from tumors of the extramedullary type, although early involvement of the vesical and rectal sphincters as a rule is indicative of an intramedullary type of tumor.

On the whole, it can be said that intraspinal tumors are removable, benign and do not tend to recur. If such a tumor is removed before irreparable changes have taken place in the spinal cord as a result of compression, complete restoration of motor and sensory loss below the level of the lesion should take place.

* Abstract of paper published in full in the *American Journal of Surgery*, 75:69-81 (Jan.) 1948

PROTRUDED INTERVERTEBRAL DISKS AS A CAUSE OF DISABLING PAIN AND PARALYSIS*

J. GRAFTON LOVE

Since Mixter and Barr established the fact that fragments of intervertebral disks could irritate and compress the root of the sciatic nerve intraspinally and produce low back and sciatic pain, the syndrome of protruded intervertebral disk has become well established. It is now known that fragments of the intervertebral disks may be protruded at any level in the spinal canal with resultant symptoms of pain, paresthesia, weakness, loss of sensation, loss of intestinal and vesical function, monoplegia, hemiplegia, paraplegia and even quadriplegia, followed by death when vital tracts in the spinal cord have been irreparably damaged.

The protrusions most often occur in the lumbar region of the spinal canal and in this region the last two disks are most often affected. As a result, the commonest symptom of protruded intervertebral disk is low back pain with or without sciatic extension.

In the cervical region the fifth, sixth and seventh disks are those most often involved; the resultant symptoms are pain in the neck, upper extremities and upper part of the chest, with or without paresthesia, anesthesia and weakness. If the protrusion occurs laterally in the spinal canal and involves only one nerve root, the distribution of the pain is in the region supplied by the nerve which takes its origin from that root. If the protrusion is large or midline in position, then the syndrome of Brown-Séquard or even quadriplegia may develop.

In the thoracic region of the spinal canal the lesion is likely to produce root pain or paraplegia, depending on the size and site of the protrusion.

Lumbar protrusions are by far the most common, constituting about 95 per cent of all protrusions of intervertebral disks in the experience at the Mayo Clinic. Since the spinal cord terminates in the cauda equina at the first lumbar vertebra, there is more room for a space-taking lesion in the lumbar portion of the spinal canal and, as a result, a lesion must become large before extensive neurologic signs develop. The intact posterior longitudinal ligament helps to maintain the intervertebral disks within the confines of the intervertebral spaces and to return the normally bulging disk to its normal shape after motion of the spinal column and after slight trauma. If trauma, stress or strain is sufficient to rupture the posterior longitudinal ligament, then the annulus fibrosus may give way and permit bits of annulus and nucleus pulposus to project into the spinal canal and remain there. Then the anatomic and pathologic condition known as "protruded intervertebral disk" occurs.

Since the lateral portions of the posterior longitudinal ligament are the weakest parts, the protrusion is most likely to occur laterally and to result in root pain if the corresponding root is irritated or compressed. If the posterior longitudinal ligament is unduly stretched or torn, but there is no

* From the Virginia Medical Monthly. 74:398-400 (Sept.) 1947.

† Root pain is pain experienced in the course of a nerve root or the nerve taking its origin therefrom and is usually aggravated by coughing, sneezing, jarring and straining at stool. It is usually worse at night.

encroachment on the nerve root, low back pain alone may result. In many cases in which ultimately operation is performed for a protruded intervertebral disk which has caused full-blown incapacity as a result of low back and sciatic pain, the physician may obtain a history of recurring bouts of low back pain or lumbago extending over a period of years. A majority of protruded intervertebral disks occur at the last two lumbar interspaces and, since this is the site of exit of the roots of the sciatic nerve, sciatic pain is the chief symptom of protrusion of a disk. If the protrusion occurs at the third lumbar interspace, the pain is likely to extend down the front of the thigh and the patellar reflex may be diminished or absent.

Protruded intervertebral disks are accepted rather generally as being traumatic in origin. The trauma may be, and often is, slight and may be overlooked or forgotten by the patient.

The acute attacks of pain resulting from protrusion of an intervertebral disk may subside on rest in bed and the application of heat to the involved part of the back. The use of diathermy is often helpful. In the more severe attacks in cases in which low back and sciatic pain or either occurs, traction on the lower extremities may be required. For protrusion of disks in the cervical region, traction on the head often proves of benefit in overcoming spasm of muscles.

In the examination in a classic case of protrusion in the low lumbar region, the patient may be found lying uncomfortably in bed or walking with a limp and with body tilted—the so-called sciatic scoliosis. The erector spinae muscles are in spasm and the normal lumbar lordosis is lost. Motions of the spinal column are painful and limited. The so-called straight leg raising test is positive on the side of the pain; lifting of the opposite extremity with the knee extended may result in pain referred to the back and to the involved extremity. If sciatic pain is present bilaterally, then the straight leg raising test is positive bilaterally. There is often tenderness along the course of the sciatic nerve. The Achilles tendon reflex is often diminished or absent. This reflex is more likely to be affected if the protrusion is at the fifth lumbar space. Some impairment of sensation in the dermatome of the root involved and some weakness of muscles may occur, but these are uncommon.

Every patient suspected of having an intraspinal space-taking lesion should receive a careful general physical examination, including examination of the blood and urine, as well as roentgenologic examination of the chest and the appropriate part of the spinal column. In addition, knowledge of the result of a flocculation test for syphilis and of the sedimentation rate of the erythrocytes may help the physician to avoid errors.

Ordinary roentgenograms of the spinal column will not give sufficient evidence on which a diagnosis of protruded intervertebral disk can be made, but they will help eliminate many other conditions which might produce a similar symptom complex.

It is my belief that no patient should have his spinal cord exposed without previous lumbar puncture. So, if the patient's general condition does not contraindicate a major surgical procedure and his symptoms cannot be alleviated by conservative measures, the next step in the examination is diagnostic lumbar puncture. This procedure may be combined with that of visualization of the spinal canal—so-called myelography.

There is diversity of opinion regarding the necessity and even advisability of performing myelography and even of lumbar puncture in these cases. My opinion is that many useless operations will be avoided and those that are necessary can be carried out more satisfactorily if the surgeon knows what the value for total protein of the cerebrospinal fluid is, whether or not he is dealing with one or multiple lesions and what the exact location of the lesion is. A value for total protein of 100 mg. per 100 c.c. of cerebrospinal fluid is seen rarely in cases of protruded disk. A high protein content usually indicates neoplasm.

If a diagnosis of protruded intervertebral disk is made, and the disk is to be removed surgically, the operation should be performed as soon as possible after lumbar puncture and after a report of the results of the spinal fluid examination has been obtained. Only that part of the disk which is fragmented need be removed. It is not necessary to curet out the disk and to try to remove all disk substance. Complete removal of all disk substance seems impossible, is dangerous and evidence secured in follow-up of patients does not indicate that it is necessary. Ordinarily laminectomy or even hemilaminectomy is not required for removal of a lumbar protrusion. After removal of the ligamentum flavum, interlaminar removal of the protruded fragments of disk is usually possible; however, one should not sacrifice safety or risk damaging the root further in order to perform this specialized technic. Until a surgeon has had considerable experience with intraspinal technics he should remove enough bone to expose adequately the involved nerve root.

If fusion of the vertebrae in the region affected is deemed necessary because of coexistence of spondylolisthesis, spondylolysis or other conditions resulting in an unstable back, the combined procedure, that is, removal of the protruded disk and fusion, preferably should be done at the same operation.

After removal of a protruding lumbar disk the patient may be up and around as soon as he feels like it, usually within two or three days. He is able to leave the hospital in seven or eight days. When a combined operation is performed, the patient is kept in bed by the orthopedic surgeons for three weeks, but no cast is used.

The operative mortality rate for protruded intervertebral disks at the clinic has continued to be less than 0.25 per cent.

The rate of recurrence of protruded intervertebral disks over a five year period is about 3 per cent. At present we do not know how, for sure, to prevent recurrences. A meticulous technic on the part of the surgeon and the avoidance of heavy lifting and straining on the part of the patient until the posterior longitudinal ligament has had time to heal are advocated.

SURGICAL TREATMENT OF HYPERTENSION*

WINCHELL McK. CRAIG

If one follows the history of surgery through the last fifty years, one is impressed with the fact that in the early stages of development, anatomy and dissection were stressed. The second era in the development of surgery involved pathology, and we have now entered into the third era, which should be called "the era of physiologic surgery." In no other condition is this so true as in the surgical approach to the treatment of hypertension and it is necessary for us to realize that the effect of the operation is in no way associated with the pathologic characteristics of the tissue removed but is associated with the physiologic effect.

The treatment of vascular disease by means of interruption of the sympathetic fibers carrying vasoconstrictor impulses opened up a new field of therapy. It was soon borne out that the functional vascular diseases, exemplified by Raynaud's disease, could be relieved, but that the other vascular diseases involving obliterative arteritis could be relieved only in so far as the vasomotor spasm of the vessels themselves and the collateral circulation could be lessened, promoting increased circulation.

This phenomenon led to the problem of the application of sympathectomy to the relief of hypertension. It has long been known that three factors involved in the maintenance of blood pressure are (1) the viscosity of the blood, (2) the power of the blood stream as initiated by the contraction of the heart and (3) the caliber of the peripheral vessels. The internists who have studied hypertension have assured us that the viscosity of the blood remains the same in hypertensive and nonhypertensive patients. The cardiographers have assured us that the impulse initiated by the heart is the same. Therefore we have assumed that there must be some difference in the size of the vessels and that vasomotor integrity plays an important part. This has been borne out by microscopic examinations of sections taken from various parts of the body, skin, kidneys, muscles and so forth, where there is a very definite narrowing of the diameter of the vessels.

To return once more to the history of hypertension, we note that Richard Bright, more than a hundred years ago, reasoned that the production of hypertension is due to altered quality of the blood, which in turn causes hypertrophy of the heart together with primary disease of the kidneys. This conclusion went unchallenged for about thirty years but at the end of this period Sir William Gull expressed the opinion that the underlying cause of hypertension is widespread vascular lesions. These two hypotheses have come down to us through the years, and in addition there have been expressions by such men as Volhard and Farr that the primary cause of essential hypertension is renal dysfunction. It would seem, therefore, that hypertension, or an elevation of the normal blood pressure, may be due to a number of different causes, or may be due to a combination of factors. And in addition to the physical factors, the neurogenic and emotional influences play a part.

The treatment of hypertension by operation on the sympathetic nervous system has stimulated a new interest in its etiology and treatment. Fifteen

* From Postgraduate Medicine. 3:60-62 (Jan) 1918.

per cent of all adults have hypertension, and 23 per cent of all deaths at an age greater than fifty years are directly attributable to this disease. Cardiovascular-renal disease, of which hypertension is an important factor, causes more than four times as many deaths as cancer, and hypertension apparently accounts for more deaths each year than does either cancer or tuberculosis. Hypertension is, therefore, one of the most common and serious conditions that come under the care of physicians, and any therapeutic innovation which may lessen the mortality rate should be given careful consideration.

It is not unusual for surgeons who are attempting to analyze their surgical results to consider the survival for five years in the treatment of cancer or other malignant diseases. Therefore, in view of the fact that hypertension simulates cancer in its mortality, it would seem that we should consider the survival over a certain period of years. In order to have some yardstick by which to measure the surgical results of the treatment of hypertension, the results obtained by medical treatment have been used. The internists have made some attempt to group the patients according to the severity of the disease and the prognosis. Patients suffering from hypertension have been examined and followed by internists, ophthalmologists and pathologists, who have estimated their life expectancy in similar fashion to the statistical evaluation of the results of treatment of cancer patients in which there has been a grading of the malignancy of the tumor.

Thus if we accept the challenge from our medical colleagues to change the mortality rate and the prognosis of hypertension over a span of five years, we must be able to show an improvement on the results of treatment by surgical means. As far as the different surgical technics are concerned, so much has been written about the different technics that it seems unnecessary to refer to them in detail. Suffice it to say that rhizotomy, extending from the sixth thoracic nerves to the second lumbar nerves, was carried out with the idea of interrupting sympathetic impulses to the splanchnic vessels and the vessels of the lower extremities. Physiologically this was sound, but the procedure also involved the motor components of the spinal nerves, a circumstance which only beclouded the picture. The operation proved to be of such magnitude and to be accompanied by so much risk, not only of death but of physical disability, that it was abandoned as being surgically hazardous. The rhizotomy operation was important owing to the fact that it proved that the physiologic interruption of the sympathetic impulses as they proceed from the spinal cord to the periphery influences the blood vessels.

This fact aroused the interest of the neurosurgeons in approaching the problem from an extraspinal route, and from this interest two procedures developed. Intrathoracic supradiaphragmatic resection of the tenth, eleventh and twelfth thoracic sympathetic ganglia and the intervening trunk, along with the corresponding section of the splanchnic nerves, has been carried out in several large series, and the patients have been followed for a period of years. The subdiaphragmatic operation, consisting of removal of the splanchnic nerves, and the first and second lumbar sympathetic ganglia, with the intervening trunk, has been also carried out in a large series with results which show a definite advance in the surgical treatment of hypertension.

Under the impression that both the supradiaphragmatic and the subdiaphragmatic types of resection of the splanchnic nerves and sympathetic ganglia had their advantages and that more extensive denervation probably would be followed by greater response, the two procedures were combined into a transdiaphragmatic type of surgical procedure. This has been modified by several surgeons until now it has been accepted as one which may be applicable to a group of patients whose conditions would not respond as well as had been hoped for when other procedures were attempted.

As one scans the literature of the present day, one is impressed by the fact that probably the combination of the supradiaphragmatic and infra-diaphragmatic procedures is being used more extensively than any other type of operation. There is no question but what the combined operation carries with it a little higher mortality rate, but as time has progressed and as the different surgeons have realized the limitations of the operation in the advanced cases and in the older group of patients, the mortality rate has been definitely lowered.

The different types of operation for denervation of the so-called splanchnic vascular bed and the vessels of the lower extremities have been developed in the different clinics. Even as much as the entire sympathetic trunk, extending from the first thoracic to the fifth lumbar, has been removed in an effort to determine the exact amount of the sympathetic nervous system which it is necessary to remove to accomplish a physiologic result. Cannon in his early experiments on the sympathetic nervous system demonstrated that in his laboratory animals a complete removal of the sympathetic nervous system was followed by some difficulty in adjusting to the difference in climatic conditions. In the patients who have had extensive sympathectomy, there have been some difficulties in adjusting to the differences in temperature and humidity in the different parts of the country. Just how important this is in the light of the effect on the blood pressure remains to be seen.

One is impressed in a review of recent literature with the fact that everyone who is doing this type of operation comes to the conclusion, after he has had sufficient experience, that the operation is physiologic and not pathologic, and that the response of the patient is in direct relation to the amount of the vascular bed involved, the extent of the involvement and the severity of the disease. Regardless of the extent of the operation, the age of the patient and the amount of irreversible tissue changes in heart, kidneys and vascular tree prove an insurmountable barrier. In considering this type of operation in the treatment of hypertension, it is of supreme importance to stress the physiologic nature of operations on the sympathetic nerves.

NEURALGIAS OF THE FACE: DIAGNOSIS AND TREATMENT*

ALFRED W. ADSON

There are two major neuralgias which are characterized by paroxysmal painful sensations of the face. The painful sensations may extend to the tongue, gums, throat and ears depending on the branches of the nerve involved. The fifth cranial nerve (the trigeminal nerve) and the ninth cranial nerve (the glossopharyngeal nerve) are the nerves afflicted. Trigeminal neuralgia occurs about seventy-five times as frequently as does glossopharyngeal neuralgia; occasionally they appear simultaneously.

Sphenopalatine neuralgia as described by Sluder may be a distinct entity though Vail preferred to refer to the syndrome as a neuritis of the vidian nerve. The pain is continuous, not paroxysmal, and is localized in the maxillary region with extension along the upper four cervical nerves. The present treatment does not offer the dramatic relief that the treatment for trigeminal and glossopharyngeal neuralgias offer to those patients suffering with the one or the other major neuralgia.

Migraine with extensions of pain along the ophthalmic branch of the trigeminal nerve is an extremely painful syndrome, accompanied by lacrimation and photophobia. The attacks of pain are not paroxysmal nor are they precipitated by touching the involved skin area.

Postherpetic ophthalmic neuralgia is a continuous painful sensation distributed to the area supplied by the ophthalmic branch of the trigeminal nerve. At the onset of the disease papules and pustules develop on the forehead, the eyelids, sclera and even the cornea. However, the severest pain develops after the skin lesions have healed. The area involved is extremely hypersensitive to touch.

The pains accompanying infections of the antrum and other sinuses are constant and continuous and are associated with symptoms of sepsis.

Localized dental caries gives rise to severe pain which is constant in character and is accompanied by local tenderness, signs of infection and roentgenographic evidence of the disease. These facts should be kept in mind when a patient comes complaining of paroxysmal pain localized in a tooth without evidence of inflammation, since the extraction of a tooth will not relieve trigeminal neuralgia.

Dental neuritis, an aching, burning pain in the gums following a complete extraction of the tooth, occurs occasionally. It is distinguished from trigeminal neuralgia in that the pain is not paroxysmal but continuous and usually involves both sides of the mouth. The gums remain tender, a fact which frequently prevents these patients from wearing their dentures. Localized dental neuritis also follows the nerve block which is employed to desensitize a part for a dental surgical procedure. Usually the pain and paresthesia disappear within two or three weeks. However, if anesthesia is a predominant symptom, it may continue indefinitely.

TRIGEMINAL NEURALGIA

Symptoms.—Trigeminal neuralgia is characterized by darting, stabbing, flashlike pains extending along one or more branches of the trigeminal nerve.

* From the *Journal of the International College of Surgeons*, 11:1-8 (Jan.-Feb.) 1943.

The paroxysms of pain usually are initiated by irritation of the region involved such as that caused by washing the face, cleaning the teeth, chewing, swallowing or talking, or by exposure to currents of air. Frequently, a particular area, commonly known as the trigger zone, is more sensitive than are other areas. Patients who suffer from trigeminal neuralgia are seen to protect the painful areas by not washing the face and by not talking, smiling or even eating in an effort to prevent initiation of a paroxysm. The paroxysm may last from a few seconds to a minute or two, and is usually followed by an interval of complete relief varying from a few minutes to several hours. The disease may occur in almost any decade of life, rarely in the first decade, and is most common after the fourth decade. The attacks of paroxysmal pain at first continue perhaps only for a few weeks, with an interval of relief for months, but as time passes, the attacks are of longer duration and of greater intensity.

It must be borne in mind that the attacks of pain may cease spontaneously; however, if the patient should be taking treatment or drugs such as the vitamins, the treatment or medication is often credited with effecting relief, when in reality the cessation of pain and the taking of medication have been coincidental occurrences. Injections of alcohol into the nerve branches and section of the sensory root of the gasserian ganglion are the only means which afford actual relief of pain.

Etiology and Pathology.—The specific etiologic agent in trigeminal neuralgia is still unknown. Horsley once attributed the disease to an ascending neuritis following dental caries. But this theory has not been accepted since neither sensory nor motor loss occurs in the nerve involved; however, paresthesia is occasionally present. Frazier, in discussing the etiology and pathology of trigeminal neuralgia, said he believed the disease to be due to sclerosis of the gasserian ganglion. Dana described the probable cause as degenerative changes in the ganglion while others expressed a belief that the changes found in the gasserian ganglion are not sufficient to make any definite statement with regard to the etiology. Pathologists at the clinic have been unable to demonstrate any specific findings. Bacteriologic studies of the gasserian ganglion under aerobic and anaerobic conditions have failed to reveal an organism which might be responsible for trigeminal neuralgia.

Since the disease occurs in cycles, with periods of remission, a phenomenon not unlike that which occurs in such diseases as angioneurotic edema, Raynaud's disease and migraine, the supposition is raised that the etiologic factor may be a histaminic or an allergic reaction of some sort. Of course, we cannot ignore the fact that the disease is more prevalent after forty years of age than it is prior to that age, which suggests that sclerotic changes in the vascular wall of arteries supplying certain cerebral centers have thus altered the function of the upper neurons of the trigeminal nerve. Though I have seen the disease develop simultaneously with syphilis and multiple sclerosis, the treatment of syphilis or the various treatments prescribed for multiple sclerosis have failed to change the course of trigeminal neuralgia.

Palliative Treatment.—Such palliative measures as the avulsion of peripheral branches of the trigeminal nerve and introduction of screws into the infra-orbital and mandibular foramina have been discarded. The

palliative treatment today consists in the use of injections of alcohol. Occasionally, dentists and a few physicians employ the technic of injecting the peripheral branches at the infra-orbital, mandibular and supra-orbital foramina but the injections that are of greatest value are the deep injections—those that are introduced where the second and third branches leave the skull. Injections into the ophthalmic branch of the trigeminal nerve are made at the supra-orbital foramen, since an attempt at injection in the orbit where the branch leaves the cranial cavity might readily affect the oculomotor nerves and produce paralysis of the oculomotor muscles. There are a few surgeons who inject alcohol into the gasserian ganglion in preference to sectioning the sensory root. The chief objection to the alcohol injection of the gasserian ganglion is that the alcohol may spread beyond the ganglion and destroy the function of the cranial nerves within the region.

New and associates of the Section on Laryngology, Oral and Plastic Surgery of the Mayo Clinic employ the analgesic method. Instead of using local anesthesia, they anesthetize the patient partially with nitrous oxide, until he passes into the analgesic state; this relieves him of the experience of pain when the needle is inserted. As the needle approaches the nerve the patient will express discomfort and then a deeper anesthesia is induced prior to the injection of alcohol. The needle employed is 8 cm. in length and 1.5 mm. in diameter and is of the trocar and cannula type; the cannula is graduated in centimeters in order to indicate the depth reached.

Injection into the mandibular branch is made at its exit from the foramen ovale; this point is reached by placing the needle through the skin at a point 2.5 cm. in front of the descending root of the zygoma, which almost coincides with the anterior bony border of the external auditory meatus. The needle is directed slightly upward along the base of the skull and a little backward at a depth of 4 cm. Injection into the superior maxillary division is carried out by placing the needle through the skin 0.5 cm. posterior to the external angle of the orbit underneath the zygoma; the needle is directed horizontally toward the anteroposterior line but it is inclined slightly upward in such a direction that it should reach the nerve at a depth of 5 cm., the point of emergence of the nerve from the foramen rotundum.

Radical Treatment.—The radical treatment consists of a partial or complete section of the sensory root of the trigeminal nerve. Many surgeons have participated in the development of the technic. At present there are three accepted methods. The most favored one, and the one most widely employed, is the temporal approach, which consists of performing either a subtotal or total section of the sensory root depending on the branches involved. There are two schools of thought concerning this procedure. The one argues that it is perhaps better to do a subtotal section, especially if only the third branch is involved, even though the disease may spread to involve the second and even the first branches of the trigeminal nerve and may require a secondary operation. The other school advocates the total section of the nerve by taking extreme care not to traumatize the ophthalmic portion of the ganglion since trauma to the ophthalmic portion gives rise to keratitis, which can be very troublesome.

The second procedure consists of performing a subtotal or total section of the sensory root of the fifth nerve by a suboccipital approach. Dandy

was an ardent supporter of this technic, arguing that if one divided the descending group of the fifth nerve, one would be able to accomplish relief of pain without producing a loss of sensation over the face. This is partially correct; however, if careful examination is made it will be apparent that, while the pain sensations are diminished to a greater degree than are the tactile sensations, not all of the pain fibers have been included in the section of the descending root of the trigeminal nerve.

The third procedure is referred to as "tractotomy," as advocated by Sjoqvist. It was designed with the idea of eliminating postoperative paresthesia, burning and creeping sensations that some patients complain of after a section of the sensory root. I regret to say that these sensations have not been relieved by employing tractotomy. There are probably indications for this procedure, especially when one is compelled to section other nerves in addition to the fifth, such as the ninth and part of the tenth cranial nerves, to relieve the pain of malignant disease of the mouth. Walker advocated tractotomy of the brain stem at a portion just above the tentorium cerebelli, whereas the Sjoqvist tractotomy was performed on the lateral surface of the medulla. This procedure did alter the pain sensation but extended this alteration to the opposite side of the body. The indications for this procedure are very limited.

Selection of Therapeutic Procedures.—At the clinic we prefer to advise patients at the onset of their disease to try, as a therapeutic test, an injection of alcohol. This accomplished two objects: First, if the patient has trigeminal neuralgia, temporary relief will be obtained. Secondly, it teaches the patient what anesthesia is like and what he must expect when the root is sectioned. If but one branch is involved, it might be wise to repeat the injection two or three times. The average duration of relief obtained from these injections is from nine to eighteen months. The first injection is more effective than the subsequent ones, but once an involvement of two or more branches develops, it seems unwise or impractical to ask the patient to return for repeated injections. Furthermore, injection of alcohol into the ophthalmic branch is not too satisfactory. The injection can be effected at a point slightly proximal to the supra-orbital foramen. It is unwise to inject much, if any, alcohol deep in the orbit for fear of paralyzing the oculomotor nerves. An avulsion of the ophthalmic branch may give temporary relief but rarely is it possible to avulse the nerve the second time; so, whenever the ophthalmic branch is involved, it is usually wise to proceed with a complete section of the sensory root.

When the patient has a history of a third or second branch involvement of rather long duration, a subtotal section of the sensory root is indicated in order to preserve the sensation to the cornea. A complete section of the sensory root at the primary operation avoids the necessity of secondary operations. However, when this is done, care should be employed to avoid injury to the ophthalmic portion of the ganglion. It is also necessary for these patients to wear a dust guard, which is snapped onto a pair of glasses, when they are exposed to dust to avoid the entrance of foreign particles into the eye on the side which has been made anesthetic by section of the root.

The sequelae that used to follow the transtemporal approach in the section of the sensory root have largely disappeared. Facial paralysis has

been eliminated by avoiding traction on the great superficial petrosal nerve which lies underneath the ganglion. This is accomplished by not elevating the ganglion or dividing the petrosal nerve lateral to the gasserian ganglion, which lies in Meckel's fossa. Meningeal hemorrhages are controlled by ligating the middle meningeal artery at the point at which it enters the cranial cavity. Hemorrhage can also be controlled by coagulating the artery and plugging the foramen spinosum with bone wax. The danger of keratitis is considerably minimized if the surgeon takes special care not to traumatize the ophthalmic portion of the ganglion.

Anesthesia follows successful injection into the nerve branches and section of the sensory root. The extent of the anesthesia depends on the nerves receiving injections and on the amount of the root sectioned. The motor root which accompanies the sensory root of the fifth cranial nerve lies under the mesial side of the root proximal to its entrance into the third branch to be distributed to the pterygoid, temporal and masseter muscles. It is essential to preserve this structure to avoid paralysis of these muscles, for if they are paralyzed, the patient will have difficulty in wearing dentures when it becomes necessary to use false teeth.

Results of Treatment.—The temporary relief obtained from injections of alcohol and the permanent relief obtained by section of the sensory root is so dramatic and welcome that patients rarely complain of the discomforts of an anesthetic face which they must accept. Paresthesia, itching and burning sensations do continue in the occasional elderly patient after root section even though the face is anesthetic to all forms of sensation. It is more noticeable in patients with low thresholds to pain. Mild sedatives offer these patients partial relief.

GLOSSOPHARYNGEAL NEURALGIA

Symptoms.—Glossopharyngeal neuralgia is a disease which resembles trigeminal neuralgia in that the pains are spasmodic, excruciating, lancinating and radiating. However, in glossopharyngeal neuralgia the pains are projected along the distribution of the ninth cranial nerve. In glossopharyngeal neuralgia the trigger zone is located in the tonsillar fossa, and the darting pains are projected toward the ear, usually terminating in the tympanum. The pains are precipitated by yawning, swallowing and talking, but they are not precipitated, as they are in trigeminal neuralgia, by rubbing the face.

Weisenburg, in 1910, was the first to describe the syndrome of pain produced by a tumor pressing on the ninth nerve. Oppenheim described a case in which there was paralysis of the ninth nerve and in which objectively there were thermesthesia and paralysis of the soft palate and pharyngeal muscles on the same side. Sicard and Robineau, Harris, Doyle, Dandy, Stockey, Peet and I have reported experiences encountered in the treatment of glossopharyngeal neuralgia.

My first experience dates back to March 18, 1922, when a patient was examined who complained of what I believed to be a rather atypical pain syndrome in the region of the tonsillar fossa, parotid gland, ear and neck, and for whom an injection of alcohol into the third branch of the trigeminal nerve had been without effect. Curiously enough, the patient said that temporary relief had been afforded when his local physician had cocaineized

his throat; at this particular time, however, this phenomenon did not have a great deal of significance to me. Since the pain was severe, resembling to some degree that of trigeminal neuralgia, I believed we were justified in carrying out a radical operation on the fifth nerve; therefore, I divided the sensory root on March 23. The patient received the usual anesthesia that follows division of the sensory root, but in spite of this, there was recurrence of pain when he yawned, about a week after the operation. The pain continued to recur until I avulsed the glossopharyngeal nerve, extracranially, through a lateral cervical wound on April 25. This gave the patient complete relief until June 10, 1924, when he had a recurrence. This led to discontinuance of the peripheral operation and to the employment of intracranial nerve section proximal to the ganglions, which I proposed in June, 1924 and carried out on November 6, 1925.

Etiology and Pathology.—The etiology of this disease is just as obscure as that of trigeminal neuralgia. It is rather curious that both diseases begin in middle life or later and that they both occur in cycles, with paroxysms of pain followed by intervals of complete relief. In both diseases no definite pathologic change has been demonstrated in the ganglions. Likewise, in both diseases the pain is invariably initiated by stimulation of a trigger zone. It is generally assumed that the disease is the result of some pathologic change in the ganglion itself. However, it is fair to postulate that these classic attacks of pain may be the result of some circulatory phenomenon, something akin to the periodic attacks of vasospasm seen in the peripheral arteries in Raynaud's disease.

Differential Diagnosis.—The pains resemble those of trigeminal neuralgia in their occurrence, duration, repetition and character, but they differ from those of trigeminal neuralgia in their distribution. The trigger zone is situated in the tonsillar fossa. The pains are brought on more often by yawning and swallowing than by chewing, and they cannot be brought on by rubbing the face; only occasionally are they brought on by rubbing the ear. Glossopharyngeal neuralgia also differs from trigeminal neuralgia in that the pain is projected from the tonsillar region and pharynx through to the ear, particularly to the tympanum. *In glossopharyngeal neuralgia it will be observed that cocaineization of the pharynx will result in temporary cessation of all attacks, but cocaineization of the pharynx will not alter the paroxysms when they are due to trigeminal neuralgia.*

Palliative Treatment.—Injection of alcohol cannot be used in the palliative treatment of glossopharyngeal neuralgia as it is used in the treatment of trigeminal neuralgia, since the ninth nerve is too intimately associated with the tenth and eleventh cranial nerves, the cervical nerves and the cervical sympathetic chain. Therefore, the only temporary procedure that has offered any palliative relief at all has been peripheral avulsion. Peripheral avulsion of the ninth nerve is a rather formidable procedure, and it is one that the writer has discontinued, since the intracranial procedures can be carried out without any difficulty and they assure permanent relief.

At the onset of this disease most patients are not prepared to accept a formidable operation. It is therefore necessary that patients thoroughly understand the problem. They should be told that the paroxysms of pain will return and that permanent relief can be obtained by intracranial nerve section. Sedatives, such as bromides, phenobarbital and trichlorethylene,

sensory root affords relief in the treatment of this type of neuralgia; as a matter of fact, the condition is aggravated by the numbness that follows section of the sensory root of the trigeminal neuralgia.

The local treatment advocated by Sluder consisted of an injection of alcohol and phenol into the region of the sphenopalatine ganglion, accomplished by injecting them through the wall of the nose under the middle turbinate. Others have advocated the use of solutions of silver nitrate, applying pledgets soaked in silver nitrate to the nasal mucous membrane underneath the middle turbinate. Vail suggested, as a therapeutic test, the use of procaine which was introduced into the sphenoidal sinus. If this gave temporary relief, he advocated unroofing the sphenoidal sinus in order to make applications of alcohol directly to the floor of the sinus, since it was his opinion that there is a dehiscence in the vidian canal which exposes the vidian nerve to infections of the sphenoidal sinus. Of late, administration of vitamins, especially niacin, has become a favored treatment. I personally must confess that I am not too sure that a true syndrome exists. If it does exist, I am not too sure about the results obtained by treatment.

OPHTHALMIC MIGRAINE

Surgery has offered very little in the control of this syndrome. Resection of the superior cervical sympathetic ganglion, as well as periarterial sympathectomy of the internal carotid, has been performed. Neither of these is too effective in relieving the pain. In a few instances in which there has been evidence of cranial trauma, I have opened the middle fossa of the skull, ligated and resected a portion of the middle meningeal artery and applied alcohol to the dura within the middle and anterior fossae with the hope of destroying the sensory fibers that ultimately communicate with the fifth nerve. The results again are rather indeterminate. Two or three have obtained satisfactory results while others have not obtained relief. Medications such as ergotamine tartrate or similar compounds have afforded some relief. Histamine therapy has still not been very effective. Much work is required before this syndrome is thoroughly understood and relief can be assured these people.

POSTHERPETIC OPTHALMIC NEURALGIA

I regret that there is no specific cure for this pain. I have avulsed the ophthalmic branch; this procedure does offer some palliative relief in that it desensitizes the scalp and permits the patient to wear a hat or cap and to wash his face without aggravating the pain. I have also sectioned completely the sensory root of the fifth cranial nerve, which has failed to give relief.

OTHER PAINFUL CONDITIONS OF THE FACE

In discussing the subject of neuralgias of the face, it is perhaps unnecessary to comment on the treatment of these other lesions. It is rather obvious, of course, that infections of the sinuses and the antrum should be recognized early and that appropriate treatment should be administered. Dental neuritis that occurs in senile patients is a rather troublesome affair and unfortunately is one that is not readily relieved. We have given injections of alcohol into the mandibular branch of the trigeminal nerve without

securing relief. Sedatives such as bromides or small doses of phenobarbital decrease the nervousness. Oftentimes, improvement of the general health of the patient by appropriate dietary regimens ameliorates the complaint. The localized dental neuritis that follows procaine block injections undoubtedly is due to the excessive amount of procaine injected into the immediate vicinity of the nerve. The symptoms of paresthesia usually disappear, and no specific treatment is indicated nor is it of value. The patient who complains about the paresthesia that follows a nerve block probably would complain more of the numbness that results from either the injection of alcohol or a subtotal section of the sensory root. Therefore, we have never felt justified in advising these operative measures.

SUMMARY

Painful sensations about the face, mouth and throat are very distressing and the major neuralgias, trigeminal and glossopharyngeal neuralgias, can become so severe as totally to incapacitate the patient. The other painful lesions of the face, as a rule, are not as severe. Their constant and continuous presence disturbs the nervous system so that sooner or later the patient will become neurotic, maladjusted and a chronic invalid.

Since complete relief can be obtained for those suffering from the major neuralgias, it is extremely important to make an accurate diagnosis, to distinguish one from the other and to distinguish them from other lesions which produce painful sensations of the face.

Though Sluder's sphenopalatine neuralgia, ophthalmic migraine and postherpetic ophthalmic neuritis are not thoroughly understood, moderate relief can be afforded the sufferers of these disorders; however, it is hoped that further investigation will bring forth measures of relief which will be as effective as those for the major neuralgias.

AN OXYGEN CONVEYER: A TOY BALLOON*

ALFRED W. ADSON

Experience at the Mayo Clinic confirms the experience of others that the unpleasant symptoms which follow encephalography, ventriculography or myelography are of shorter duration when oxygen is used instead of air as the contrast medium. Knowledge of this fact and a desire to avoid setting up cumbersome apparatus or moving gas tanks from room to room prompted me to employ the procedure herein described for conveying oxygen.

The materials required for constructing the device are 6 feet (182.9 cm.) of rubber tubing, a glass tube, 3 inches (7.6 cm.) long, filled with absorbent cotton to serve as a filter, six stopcocks and a dozen or two toy balloons. One end of the stopcock is such that it will admit the nozzle of a Luer syringe; the other has a corrugated surface over which the neck of the balloon is slipped and tied in place.

* From the Journal of Neurosurgery. 4:326-327 (July) 1947.

The surgical nurse ties on several balloons in preparing the materials for sterilization. All materials, including the portable yoke for the oxygen tank, are autoclaved.

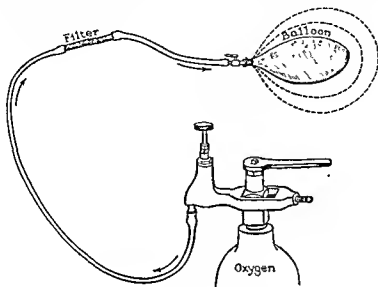


Fig. 111 — Filling a balloon with oxygen

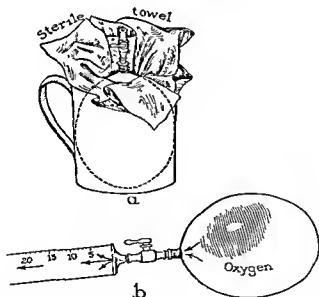


Fig. 112a.—A filled balloon ready for use; b, oxygen being withdrawn from a balloon through a Luer syringe

On the morning of operation the nurse fills, under aseptic conditions, as many balloons as will be needed, including an extra one which would be

available in the event of breakage. In assembling the parts, a second nurse thoroughly cleanses the head of the gas tank with alcohol prior to adjusting the yolk and operates the lever as each balloon is filled (fig. 111). The filled balloons are stored on the reserve instrument table. As they are needed they are carried in a sterile receptacle to the room in which the oxygen is used (fig. 112). The oxygen is transferred with a syringe from the balloon to a spinal puncture or ventricular needle as required.

During the war we substituted rubber gloves for balloons. Except for their odd appearance, rubber gloves are more efficient than balloons since they can be autoclaved many times more than balloons without disintegration.

Space does not permit discussion of the use of air, oxygen or helium in studies of the brain and spinal cord. However, readers are urged to review the paper by Cleveland and End. Our experience at the clinic has encouraged us to use oxygen as a contrast medium in roentgenographic studies and to give, after such use, inhalation of pure oxygen for three to six hours.

THE CENTRAL NERVOUS SYSTEM IN PERIARTERITIS NODOSA*

HARRY L. PARKER AND JAMES W. KERNOHAN

Oversimplification is sometimes worse than obscurity but in the relatively short time given, all we can do is to deal with the skeletal facts. There were available for this present study the records of necropsy in thirty cases of periarteritis nodosa and examination of the brain and cord was available in sixteen of these. One of us (H. L. P.) studied the clinical records of these sixteen cases with a view to finding in what proportion evidence of damage to the central nervous system was found. Further, an attempt was made to determine how many patients complained primarily of symptoms referable to the central nervous system. This clinical study was done without reference to the pathologic findings and it was only afterward that these findings were compared with the pathologic findings of the other of us (J. W. K.).

As usual in this disease it was obvious that, with so many bewildering and multiple signs and symptoms, a rigid form of classification would be impossible. Roughly, however, the cases fell into three groups. The first consisted of five cases in which the signs from the beginning to the end were very largely those of polyneuritis with involvement of other organs but without evidence of disease of the central nervous system. As one would expect when referring later to the pathologic findings, in only one case was evidence of arterial disease of the brain or spinal cord found and this was slight.

The second group of cases were those in which there were symptoms and signs of disease of the central nervous system, but they came as terminal events and could have been caused by hypertensive encephalopathy or uremic poisoning. These cases were four in number and generally the clinical

* Abstract, published in full in the Transactions of the American Neurological Association. 72: 54-57, 1947.

picture throughout was one of cardiovascular-renal disease. Periarteritis of the nervous system was present in all of these four cases but not to any extent in the degree which was found in the last group.

In the last group of seven cases, the more important one in view of the present discussion, clinical signs of manifest disease of the central nervous system were present almost from the beginning. The first two patients were relatively young and the clinical picture was that of an acute infectious disease of the brain. There were fever, leukocytosis and large numbers of polymorphonuclear leukocytes in the spinal fluid. The course was short and correspondingly the period of observation was short. The clinical impression given by these two patients was that they were suffering from multiple cerebral abscesses. There were three patients whose disease was of a more chronic nature, consisting of polyn neuritis with bulbar or cerebral symptoms. The impression was that one was dealing with diffuse neuronitis. Death occurred in these cases mainly as a result of renal insufficiency. The last two cases were possibly the most interesting of all these studied. In the *first case the picture was that of a rapidly growing glioma of the brain*. There was nothing whatever to suggest a diffuse infectious process. The patient in the other case was elderly and had all the signs of peripheral and cerebral arteriosclerosis. The course of the disease was rather short and the picture was that of thrombosis of the basilar artery and pontine vessels. In our opinion in these two cases the correct diagnosis could not have been made while the patients were alive.

In the sixteen cases in this report the central nervous system was available for study. In twelve or 75 per cent of sixteen cases the changes in the arteries were characteristic of periarteritis nodosa. The arteries involved varied from case to case. In some the vertebral system of vessels sustained the brunt of the lesion while in others, it was the carotid system and in still others both systems were involved. In some the meningeal vessels alone had the histologic picture of periarteritis nodosa, in others only the vessels in the substance of the brain and in a smaller group both the meningeal and cerebral vessels were included in the process. Lesions in the arteries varied from very early ones through those in various stages of the healing process to completely healed ones, although rarely were all stages found in the same case. It was interesting to note that rather frequently the size of the vessels involved was constant throughout the central nervous system in each case. With the afore-mentioned variations in location and age of the disease process, one would scarcely expect anything but an extremely varied clinical picture in such a group of patients.

The conclusion to be drawn is that of others—that the diagnosis of periarteritis nodosa must be made on the basis of the collective signs and symptoms of many organs of the body involved simultaneously or consecutively. This study was made to show, on a background of a small group of cases, what possible diseases of the central nervous system may be presented for diagnosis without a hint as to their nature. Many cases have been reported elsewhere in which periarteritis nodosa could not be diagnosed and the disease manifested itself as almost any type of affliction of the central nervous system. Generally speaking, in our group, at best, the diagnosis could have been made or could have been suggested in a major proportion of cases with, of course, the exception of the last two described in the last group.

PSYCHOSOMATIC MEDICINE THAT EVERY PHYSICIAN SHOULD KNOW*

WALTER C. ALVAREZ

Every physician must know much about psychosomatic medicine if he is to avoid making many diagnostic mistakes, ordering many futile operations, and scaring half to death many organically sound patients.

He must see that many of his patients are ill because of inborn nervousness, constitutional frailness, excessive worry or excessive strain. He must see also that none of the tests on which he so relies for a diagnosis will reveal a neurosis or psychosis or nervous breakdown. There is still great need for taking a good history and for sizing up the patient.

Many discomforts in the thorax or abdomen arise in the brain and are referred out to the periphery. Most of the feelings of chronic fatigue and ill health probably arise in the brain.

Some idea of the great importance of psychosomatic medicine can be seen from the facts that about one of every seven drafted men who passed the physical tests had to be rejected for mental reasons; about one person in thirteen in this country is insane or in need of psychiatric help, and one in nineteen will eventually be committed to a state asylum.

For every one of these persons there are several near relatives suffering from equivalents of insanity, such as chronic invalidism, unemployability or alcoholism. These are the "chronics" who fill physicians' offices.

Physicians have long thought insanity was no concern of theirs; today they are beginning to see that from the fringes of the huge reservoir of psychopathy they are getting a high percentage of their most troublesome patients. Today, physicians are beginning to see that there is a type of psychiatry that is their concern and which they must practice.

Recently three important points have come home to the medical profession: (1) that a poor nervous inheritance, unhappiness and strain can cause neuroses; (2) that they can bring to light organic disease or cause flare-ups of such disease, and (3) that in many cases of organic disease the symptoms are all those of a complicating neurosis.

A study of consultant practice and the many poor results of abdominal surgery shows that as yet there is still great need for improvement in the recognition of neuroses and the avoidance of futile laparotomies.

One cannot trust one's ability to diagnose a neurosis or psychosis by exclusion because too many inconsequential findings are disclosed by the examinations. One of the greatest arts needed in medical practice today is that of disregarding findings which cannot explain the symptoms.

Every good physician must, willy-nilly, become a psychiatrist.

What is to be done to improve matters? The family physician must more often stick to his strong impression that the patient is neurotic and the syndrome functional in nature. All physicians need more training in recognizing promptly the common neuroses just as they recognize whooping cough the minute they hear it. They must recognize nervous breakdowns, tired vision, air hunger, hyperventilation, globus, nervous whispering.

* Abstract of paper published in full in the *Journal of the American Medical Association*, 155:704-708 (Nov. 13) 1947.

palpitation, regurgitation, abdominal quivering, repeated belching, heartburn, nervous bloating, the "sore colon" syndrome, nervous diarrhea, nervous types of pain, the nervous bladder, psychosomatic rheumatism, migraine, the "nerves playing tricks" syndromes, and equivalents of epilepsy.

When it comes to treatment the physician must resolve never again consciously to use placebos of diagnosis. When he says the trouble is functional he must go on taking a history until he knows what one of twenty or thirty types of functional trouble it is. Only then can he treat intelligently and successfully.

Many persons with nervous troubles can be greatly helped by any friendly sensible, philosophically inclined physician. The worst ones should be sent quickly to a psychiatrist.

PREVENTIVE MEDICINE AND MONGOLISM*

C. ANDERSON ALDRICH

Once in every 500 deliveries the attending physician is faced with a potential family tragedy in the birth of a mongolian idiot. This incidence is true in the United States and, while I am not familiar with the actual statistics in reference to babies of other countries and races, it is a well-known fact that mongolism does occur in people of every land and of all colors.

I recall an incident which happened only a few years ago while I was making ward rounds with a visiting Chinese physician. We came to the crib of a small infant named Wang. I said, "Here is a Chinese baby." Immediately he flashed back, "Ah, but he's a mongol too." He was right and his quick reply taught me that it was no more difficult for a doctor familiar with Chinese babies to differentiate the mongolian idiot than it was for us to do so in Caucasian infants.

The problems presented by the arrival into a family of one of these accidents of development are many and of deep concern to the baby, his parents, physicians, social workers and various officials of the state welfare and health departments.

From the baby's point of view several points should be mentioned. The mortality rate in the first two years of life is high because of the inferior musculature of these children. Infections of the respiratory tract are particularly dangerous and congenital heart disease is very common and a frequent cause of death.

From the standpoint of the child's living an adequate social life the prognosis is even worse. I have often remarked that the better they were, the worse off they were. The inadequacy which is inevitable in mongolism is not so noticeable if the child is an evident idiot and if he is treated appropriately. But when he almost "makes the grade" and tries to enter freely

* From the American Journal of Mental Deficiency, 52:127-129 (Oct.) 1947.

into the competition of civilized living, his experience is usually devastating and may lead to serious social situations, as you well know. The child is constantly being frustrated by his inability to compete and to comprehend his difficulties. The troubles met in dealing with mongols, however, would be much worse were it not for his well-known sunny disposition. I have often thought that in this world of strife and trouble mongolian idiots, of all human beings, perhaps live the most carefree and happy lives. Nevertheless, they are happiest when allowed to grow up in situations where they compete with their peers, in institutions.

The difficulties faced by the mothers of these children are, in many respects, more serious than those faced by the child. Because the mongolian is so incompetent in the ordinary technics of living, his mother soon becomes a complete slave to his dependency. As a result, she devotes all of her time to his necessary care, neglecting her other household duties, her other children if there are such, and inevitably, her husband. The effect of all this is that all other satisfying areas of living are blotted out and that she becomes enmeshed in an almost hopeless entanglement of emotional ties to the mongol. From the practical standpoint, a potentially useful citizen is removed from social intercourse. It is a clinical fact that few such mothers have subsequent children.

In many instances, the father is placed in a very trying situation. When the realization gradually seeps into his consciousness that all is not well with his child, he may notice also that his wife is becoming so engrossed with her baby that she is losing touch with him and all his areas of interest—that she has no time either for his affection or for the outside recreation they used to enjoy together. If he faces facts and tells her his fears, she often feels that she and her child are being attacked and responds with a defensive emotional storm. If he says nothing, they usually drift apart slowly. Many separations and divorces follow the birth of mongolian idiots.

The other children in afflicted families suffer from a social stigma which they and their playmates sense but often do not understand. With passing years, as the mongol becomes less and less acceptable in the neighborhood groups, his brothers and sisters refuse to bring other children into the house, of necessity play elsewhere and are obsessed with a feeling of family shame no matter how unjustifiable it may be. Few situations are worse for household morale or for that of the children.

There is an economic element in this situation also. When parents finally realize the deficiencies of their child, they often begin a hopeless round of visits to doctors and clinics near and far, spending all of their savings and often borrowing up to their capacity in the vain hope of finding a cure. It is a sad commentary on human nature to note that not infrequently they encounter people who promise much and slowly drain the family's resources in fantastic and useless methods of treatment.

There is only one adequate way to lessen all this grief, fortunately a measure which most experienced physicians will agree to, and that is immediate commitment to an institution at the time of diagnosis. But this procedure is difficult to accomplish if the mother has had the child under her care for any prolonged period. She becomes so necessary to the child and so attached to him that she cannot give him up. Therefore, it becomes highly important to make the diagnosis as early as possible. Fortunately

this can be done in more than 90 per cent of the cases on the day of birth. I am outlining here a technic which has been found successful in accomplishing separation of newborn mongols from the family, in the hope that it may help others in meeting this tragic situation.

1. When the diagnosis has been made in a newborn the mother is told that the baby is not strong enough to be brought to her at present and that he must remain in the nursery for a few days.

2. Next, the father is asked to meet the physician immediately, bringing with him any close relatives who are available in the neighborhood. At this conference, the nature of the problem is explained in detail, emphasizing its seriousness, the facts that no one is to blame, that future babies will be normal and that immediate placement outside the family provides the only hope of preventing a long series of family difficulties.

It may be advisable, in many instances, to enlist the aid of the clergyman closest to the family. This has been of great help to me several times, for often the pastor will be familiar with the unfortunate sequence of events which accompanies the birth of a mongol and may have dealt with such disrupted families in his church. He is often eager to prevent any repetition of such tragedies.

3. If the father and close relatives of the family can be made to accept outside placement as the solution of their problem, the physician and the husband, backed up by the family decision, report the whole situation to the mother. She is asked, not to make the decision, but to accept the one which has already been made by the close relatives. This has the advantage of tending to prevent the quite natural feelings of guilt which might otherwise plague her after surrendering the child to another's care.

4. Having obtained unanimous family permission, the physician must arrange for immediate placement of the infant. In some states this can be done through public agencies without delay. In others a boarding home placement for the interval is necessary until the delays incident to commitment and finding institutional vacancies have been overcome.

This method is, of course, not infallible, but in the past fifteen years it has failed me only two or three times. It means that the physician must take the lead in precipitating an immediate crisis in order to prevent much more serious difficulties later on. This is preventive medicine.

I am presenting this report to you with the idea that it may stimulate interest in making available a rapid means of committing mongoloid infants to institutions. There is no doubt but that the social service load in any community could be lightened were cribs made available for immediate occupancy by newly born babies who were mongolian idiots.

UNAPPROVED BEHAVIOR OF INFANTS AT ONE YEAR OF AGE: MOTHERS' APPRAISAL BASED ON 668 CHILDREN*

C. ANDERSON ALDRICH

In a review of the records of 668 babies, all of whom were born in 1944 and 1945, and whose one-year-old check up had been completed, the mothers' answers to the question, "What habits does your baby have of which you do not approve?" were studied. The following points were noted.

First, the question was answered in 623 records.

Second, the mothers of 421, or 68.2 per cent of the babies, replied that there were no disapproved habits.

Third, the mothers of 199 babies reported that disapproved habits were noted 216 times and these comprised forty different items.

Fourth, these forty items were classified as follows: repetitive habits (153), self attack (22), resisting routines (17), attack on others (13) and expressions of unhappiness (11).

Fifth, thumb-sucking occurred 137 times; it constituted almost 63 per cent of all the complaints.

COMMON BEHAVIOR DISTURBANCES IN THE FIRST TWO YEARS OF LIFE†

BENJAMIN SPOCK

Significant behavior disturbances in babies are relatively infrequent during the first year as compared with the second, mainly because there are relatively few occasions for conflict between mother and infant. On the other hand, anxiety and weeping spells are common in the mother at the start. In our civilization she may take her first baby home without any previous experience to accustom and reassure her. Prenatal classes are of some value but do not take the place of that everyday familiarity with the live baby which is the lot of young women in cultures more primitive and communal than ours.

A number of pediatricians, psychiatrists and obstetricians have recently become interested in the possibility of making the lying-in period more natural and reassuring. They have felt that the usual practice of relegating babies to a nursery, from which they are brought to their mothers only at intervals, and the tendency to let breast feeding go by default have inadvertently given the inexperienced mother the initial impression that she is of little importance to her baby and that its care can only be entrusted to medical experts. The so-called rooming-in arrangement is being experimented with in Detroit and elsewhere. The baby's crib remains in the

* Abstract of paper read at the meeting of the American Public Health Association, Atlantic City, New Jersey, October 6 to 10, 1947.

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mother's room so that she can become familiar with his noises, moods, movements and appetite, and so that she can feed him on the breast when he is hungry rather than according to the clock. Preliminary reports suggest that the effect is good, not only on mothers and babies but also on fathers. In our conventional obstetric arrangements the father is apt to feel like a rank outsider, a germ carrier from whom the baby must be shielded. In the "rooming-in" arrangement, he and he alone is allowed to visit, which allows him to think of himself as an acceptable member of the family at this formative stage of his development.

There has been a growing tendency in the last few years to discard the rigidity of feeding schedules, which in the past has probably done harm in encouraging mothers to become tense and arbitrary. A number of pediatricians are now recommending that the baby be fed when he seems hungry, irrespective of the hour. Although the method has a solemn name, "the self-demand schedule," and sounds newfangled, it is obviously Nature's own, which was used by the entire human race until the turn of the century. A better term might be "self-regulated schedule." Surprisingly, or perhaps not so surprisingly, most babies are found to work themselves onto a fairly regular schedule in a short time. "Rooming-in" and "self-regulation" appear to be of real value in maintaining the mother's self-confidence and giving her a relaxed attitude toward her child.

Feeding problems are the commonest ones during the first year in our culture. A few are started in the first weeks of life if the formula prescribed proves too large and if the nurse or mother has been encouraged to be arbitrary. The baby who, every time he falls asleep satisfied, gets the soles of his feet snapped and the nipple stirred vigorously in his mouth begins to lose his enthusiasm for food and to become balky and irritable. If the resistance to feeding becomes well established it may last for years and have a harrowing effect on the personalities of child and mother.

A more common time for feeding rebellion is when solid foods are first introduced. A majority of infants, despite their eagerness for calories, are initially doubtful about the first solid food. The taste, the spoon, the consistency, the method of swallowing are all new. Most of these skeptics decide after a few days that the substance is at least nutritious and they gradually develop more enthusiasm. An appreciable minority, however, become increasingly intolerant as the days go by. If the struggle is kept up, the mother may report, at the end of ten days, that the baby is beginning to refuse his beloved bottle too. This spreading of the hassle is a common phenomenon in children's disorders.

Attempts at forced weaning for which the baby is not ready often cause bad feeling. Psychiatrists have emphasized the danger of too early weaning, especially from the breast. But the exact pathogenesis of a weaning disturbance as seen by the pediatrician is not a simple matter of earliness or of deprivation of the breast. In the first place a majority of young infants who are nursing at both breast and bottle show their ignorance of what is theoretically best for them by preferring the bottle. On the other hand, the baby who has been entirely breast fed for the first three or four months of his life is likely, if the breast supply is plentiful, to object violently to letting a rubber nipple pass his lips, and may prefer to starve for several days.

Some bottle fed babies show a readiness for gradual weaning to the cup in the period between eight and twelve months. They become less eager for the bottle, stop to play with the nipple, and take milk readily from the cup. On the other hand, an appreciable number, even though they have taken willingly a little milk from the cup from as far back as five months of age, will, as they get to be about nine months old, bat the cup away suspiciously or, pretending they have forgotten what to do, let all the milk run down the sides of their chins. It would seem as though a shrewdness coming on at this stage of development makes them suspect and fear that the bottle is about to be taken away. These are the babies who are generally devoted to the bottle, eyeing it during the solid part of their meal, stroking it and murmuring to it as they drink the contents to the last drop. Forced deprivation of the bottle at such a phase is likely to produce prolonged refusal to take any milk from the cup, unhappy behavior for a number of days and sometimes a complete hunger strike until the frightened mother gives in.

Breast fed babies, on the other hand, rarely balk at weaning from breast to cup in the last quarter of the first year. In fact, they tend to wean themselves, nursing for shorter periods and gladly taking increasing amounts from the cup. There appear to be at least two reasons why they are more willing to be weaned than are bottle fed babies of this age. Breast and cup are less similar than bottle and cup. It is the shift to something similar that an opinionated baby resists. Another factor is the nine-month old baby's desire to be independent during meals. He is now likely to want to sit up for his spoon feeding, and if he is bottle fed, to take the bottle away from his mother's hands and to drink the whole contents while sitting bolt upright. In other words, the breast fed baby may prefer to wean himself not so much because suckling has lost its charm but because he has advanced to the stage where he is impatient in the dependent, cuddled position.

The second year brings marked changes in an infant's personality and behavior, and calls on the mother for entirely new resourcefulness and adaptability. She has become accustomed during the first year to his automatic co-operation. If she offered a teaspoon of spinach he opened his mouth as eagerly as for applesauce. Even though he liked it less he was too hungry to quibble. If it was convenient for her to have him in the playpen she could put him there, toss him a couple of familiar toys and know that he would play happily. But at about a year he acquires independent locomotion, and with it a charge of energy that keeps him going all day. He explores constantly, shakes table legs, pulls lamp cords, removes every book from the bookcase, climbs on anything he can reach. His ego is taking definite shape. He senses he is a separate person entitled to wishes and a will of his own. He early learns to say "No" and uses it on all occasions, even in response to suggestions that appeal to him. He has learned no respect for authority and when told "No, no" from across the room is more likely to persist than desist. It seems as though he has a compulsive need to exercise his will power for its own sake.

As he becomes more insistent on his independence from his mother, he simultaneously becomes aware of his dependence. He may cry each time she leaves him alone. If he is allowed freedom to explore in the house, he scrambles back to her at regular intervals for reassurance. In the doctor's office he, who at eleven months was quite unconcerned about examination,

now leaps to his feet and yelling, tries to climb off the table into his mother's arms. He is now likely to be frightened by noisy, moving objects like vacuum cleaners. Undoubtedly, it is part of his total pattern of emotional development that, when he has the ability and the desire to explore away from his mother, he also has the instinct to hurry back to her noisily when he meets something strange and potentially dangerous.

A majority of babies around the age of a year show the same exaggerated arbitrariness in appetite that they show in other matters. Probably the smaller rate of weight gaining and the discomfort of molar teething play a part in the sudden decreases in appetite that occur. But over and above these he shows an irritating choosiness. He refuses to touch the vegetable which yesterday was his favorite. He may turn against all his vegetables for weeks and even months at a time, or against cereal and his milk. The conscientious mother, sure of the importance of the balanced diet, is tempted to become bossy and insistent. The child's temporary dislikes of certain foods are turned into permanent hates which often last for years. *Certainly more feeding problems begin during the second year than during any other period.* The irritation of the frustrated mother and the balkiness of the child easily spread into other aspects of their relationship.

Psychiatrists from data gained from older children and adults have stressed the danger to the child's emotional development of too early and too rigorous toilet training. Pediatric observation would indicate that the earliness at which training efforts are begun is much less important than the reaction of the child and the attitude of the mother during the precarious second year. He is generally opinionated and touchy. He becomes increasingly aware of his bowel function and takes a possessive and proprietary attitude toward it. As he slips off the seat he turns to admire his movement, *sniffs it appreciatively and asks his mother to enjoy it too.* If her attitude is overdemanding and intolerant it is easy to see why she rubs him the wrong way. Actually, few revolts occur in the babies whose movements are naturally regular. They have their movements on the seat right after breakfast before they have a chance to become impatient. It is the child who is naturally irregular whose mother is tempted to put him on too often and insist that he stay on too long. The babies who are most prone of all to develop resistance are those who have experienced painfully hard movements. In fact, one painful movement may be enough to create a dread of the toilet that lasts six or eight months. Whatever the cause of the initial resistance, the mother's insistence increases the child's *obstinacy, anxiety and guiltiness.* When he eventually decides to give in and perform in the right place, he may show anxiety about other forms of dirtiness too. Suppositories and enemas used after a training struggle has begun are resisted with rage and terror and hasten the character distortion.

This vital phase of ego formation is difficult for parents. They are not prepared by experience or teaching for the drastic changes. Arbitrary doctrines about diet and toilet training invite them into trouble. Small houses and apartments provide too few cubic feet per ego and too few harmless outlets for the expanding personality of the one-year old child. The small number of children per family encourages parental overconcern. There tend to be too many prohibitions, too many demands and too many clashes. The child's outgoingness is blocked, his progress toward independ-

ence is impeded and his awareness of self is intensified beyond what is ideal.

If the mother is a stable, affable sort of person, she finds ways to get along with this new child, even if she has to go against current dogma on diet, toileting and discipline. But the insecure mother or the dominating mother is easily thwarted. When she finds that a little scolding or shaming doesn't work, she redoubles her efforts. The self-frustrating mother even creates issues by reminding her one-year old not to touch something, before he has thought of doing it.

In the olden days, parents with poor leadership qualities probably relied most on slaps. But the modern teaching that physical punishment is shameful has deflected them into forms of control such as chronic scolding, prolonged moral disapproval, warnings of the dangerous consequences of misbehavior, even excessive reasoning and overexplanation, which I believe bring about worse distortion of the malleable personality. These influences are manifested by the age of two years in tense, anxious, dependent, self-centered children, and lay the groundwork for the formation of specific neurosis and character disorders.

Although the pediatrician cannot hope to change the mother's basic nature, I believe that he can give her prophylactic advice that minimizes the clashes. He should explain at the start that the baby will be a better judge than mother or pediatrician of how much he needs at each feeding, warn the mother when starting solids to give the child time to get used to them, and advise against weaning until the child shows readiness even though it isn't until the middle of the second year. He can explain, before the age of a year, that appetite is likely to change and that satisfactory substitutes which the child likes can be found. More pediatricians today are advising mothers to omit all toilet training efforts until toward the end of the second year when the baby's awareness of bowel function and intense desire to imitate may induce him to think up the idea of going to the toilet himself. At least the mother should be warned against beginning her training efforts until she can exactly predict the timing of the movement, either because of the baby's regularity or because he begins to make some sign of readiness. It is possible to help the parent who is unimaginative or insecure to avoid some of the disciplinary clashes by describing how the house must be arranged so that most breakable objects are removed from reach, and enough harmless ones like pots and pans and magazines left near the floor. Then the housebound child has enough to occupy him without too many prohibitions. When inhibition is started, the main recourse of the parent should be a brisk, friendly removal of the child from the dangerous or breakable object and distraction to something else. Mothers also need to be urged to take small children outdoors often, to let them out of their carriages in places where they can safely be given some freedom and where they can become accustomed to other children.

We need also experimentation with some sort of guidance nursery or guidance playground where one and two-year olds, too young to be left at nursery schools, could come to play. Their mothers could look on, learn from each other and have the opportunity when they felt the need to ask advice from an expert nursery school teacher or psychiatric social worker in attendance without having to go through the formality of making an appointment.

OBSERVATIONS ON THE TREATMENT OF RECURRING
CONVULSIONS (EPILEPSY) OCCURRING
AMONG CHILDREN*

HADDOW M. KEITH

The treatment of recurring convulsions (epilepsy) is a difficult problem since there are many variables, and treatment must take place over a long period of time. The etiology of such convulsions is, of course, extremely important but in the majority of cases this cannot be determined with accuracy and one is forced to treat the symptom without being certain what the underlying pathologic disturbance is. Even when the latter is recognized, it is frequently impossible to remove or alter the fundamental abnormality and treatment must again be directed toward the symptom.

It is essential that mental hygiene be considered in the treatment of epileptic patients. In certain cases emotional and mental stresses may well be precipitating factors in the attack. Repeated discussions with parents or other members of the family may reveal that the patient has conflicts and anxieties, not otherwise noted, and tensions may be relieved with much benefit to the child. A tactful social worker or a schoolteacher who is in close contact with the family may be of great help.

It is often questionable whether a child who has convulsions can or should go to school. The decision will, of course, depend to some extent on the frequency and severity of the attacks. If the attacks occur rarely or are well controlled by drugs or diet, attendance of an ordinary school is advisable. If the attacks occur more frequently or are severe, it is better to have the child attend a special school or a public institution for epileptics. However, his education should proceed as nearly normally as possible and his social environment and activities should be, as nearly as possible, those of the child who does not have convulsions.

While perhaps not all workers will agree, it is widely considered at the present time that an epileptiform attack is due to an "explosion" of abnormal impulses in some portion of the brain, causing disorderly responses in the body, frequently accompanied by loss of consciousness. This presupposes an abnormal irritability of a portion or portions of the brain. Most forms of treatment have been directed toward reducing this increased irritability and the resulting "explosion," and drugs which have a sedative or anticonvulsant action have been used most frequently. The object of treatment is the complete prevention of seizures, with as little interference as possible with mental and emotional development, as well as physical activity.

One of the earlier and more successful of the drugs used in this manner was bromide. Lacombe reported its use as early as 1853. The next effective drug to be used was phenobarbital which was used first in 1912. This is now rather well known and widely used. Later, methyl ethyl phenobarbital (mebaral), a methyl compound and a near relative of phenobarbital, was introduced. In 1938 Merritt and Putnam advised the administration of diphenylhydantoin sodium (dilantin sodium). These four drugs may be used singly or in combination.

* From the *Journal-Lancet*, 67:449-450 (Dec.) 1947.

Most physicians rely on these few drugs for therapeutic effect, although many other drugs have been tried. In addition, at the Mayo Clinic, we have used the ketogenic (high-fat, low-carbohydrate) diet since 1921 and I wish to report some of the results of this treatment of patients who have been observed for many years. It is an effective treatment for children but not very effective for treatment of adults.

PRESENT STUDIES

In an attempt to compare the results of treatment with drugs and ketogenic diet, 300 consecutive cases in which the patients were first examined in 1940 and 1941 were studied. The patients were all fourteen years of age or less when they were examined at the clinic the first time. The results were classified as follows: Patients who had no attacks of any kind so far as they knew from the beginning of treatment or shortly thereafter until the end of the follow-up period (between four and five years) were considered to be well. Patients whose condition was definitely improved either for a comparatively short time or for a much longer time but who still had some difficulty were considered to be improved, and the remainder who continued to have attacks in spite of reasonable treatment were considered to have received no benefit.

Follow-up information was not obtained from 113 patients. Of the remaining 187, thirty-eight had gross neurologic disorders, such as cerebral palsy, marked mental retardation and so forth. Seventeen of these thirty-eight patients improved as far as their attacks were concerned; eight of them improved on treatment with phenobarbital alone; four improved when dilantin sodium was used; three, when a combination of the two was used, and one improved as the result of use of the ketogenic diet. One patient became well without any treatment and remained so for four years. Two children in this group died during treatment, one from general paresis and one from rather severe hydrocephalus.

One hundred forty-nine of the patients had no handicap but the convulsions and were treated for four to five years. Some of these 149 patients were treated by more than one method at different times. This makes the total number of patients who received the various types of treatment more than 149. In the remarks concerning treatment when I refer to use of only one type of treatment I mean that that was the only treatment given at the time.

Thirty-seven of the 149 patients received ketogenic diet only. Of these thirty-seven, ten (27 per cent) were completely well, sixteen (43.2 per cent) were improved and eleven (29.7 per cent) were not benefited. A group of fifteen patients received ketogenic diet plus drugs. Again, four (26.7 per cent) were well, three (20 per cent) were improved and eight (53.3 per cent) were not helped. The ketogenic diet was maintained until the patient had been free of attacks for one year or more; then the diet was changed gradually to a normal diet containing usually a moderately limited amount of carbohydrate. When drugs were used in addition to the diet, their use usually was continued after the change in diet had been made.

Forty-eight patients received phenobarbital alone. Of these, six (12.5 per cent) were well, but continued to take full doses of medication. Thirty-

one (64.6 per cent) improved for periods varying from a few months to four years.

Fifty patients received dilantin sodium alone. Six (12 per cent) remained well while taking the drug, nineteen (38 per cent) were improved, and twenty-five (50 per cent) obtained no help. It is interesting to note that twelve patients (24 per cent) of this group had toxic reactions and this was the only group in which evidence of toxicity was found.

A final group of twenty-six patients received both phenobarbital and dilantin sodium. Three patients (11.5 per cent) were well while taking medication consistently, twelve patients (46.2 per cent) were improved and eleven (42.3 per cent) were not improved.

A further group of cases studied consisted of all those in which treatment with the ketogenic diet alone or with drugs was started between 1921 and 1930. The records were studied through 1945. This group consisted of 311 cases. Seventy-three of the patients did not co-operate well enough to allow us to determine the therapeutic effect of the diet; forty-eight had gross neurologic lesions, including one brain tumor. As far as could be determined 190 patients gave the diet a fair trial. Sixty-seven patients (35.3 per cent) remained well after this treatment for periods of from four to twenty-two years. Thirty-five patients (18.4 per cent) were definitely improved, so much so that they were willing to continue the diet for several years.

Thus, by means of a ketogenic diet 53.7 per cent of the patients treated who had so-called idiopathic epilepsy were influenced favorably and 35.3 per cent have been well for long periods (four to twenty-two years).

The inheritance of epilepsy is a subject upon which much has been written. It is not within the scope of this paper to discuss the arguments. Penfield and Erickson stated that "the conclusion cannot be avoided that some potential or latent germ plasm defect or vulnerability is inherited." In this connection it is of interest and perhaps of value to point out that twenty-nine children were born to twenty of the 190 patients who were followed up. The ages of the twenty-nine children ranged from a few months to twelve years at the time this study was made. Not one of these children had been observed to have convulsions of any sort.

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RADIOLOGY AND PHYSICAL MEDICINE

THE ROENTGENOLOGIC DIAGNOSIS OF DIAPHRAGMATIC HERNIA*

B. R. KIRKLIN

Broadly speaking, the diagnosis of diaphragmatic hernia is essentially a roentgenologic problem. At the Mayo Clinic, 90 per cent of these hernias are found more or less unexpectedly at routine examinations of the stomach, or more rarely of the colon, to determine the cause of gastro-intestinal symptoms. In the remaining 10 per cent of cases the patient comes with the diagnosis already made, or the clinical history is suggestive of hernia, or routine roentgenograms of the thorax reveal abnormalities that may be due to hernia and accordingly call for further roentgenologic investigation.

In all roentgenologic examinations of the stomach the possible existence of diaphragmatic hernia should be kept in mind by the examiner, and his standard technic should provide for that contingency. Since a vast majority of hernias are at the esophageal hiatus, the region of the esophagogastric juncture should invariably be inspected thoroughly while the first two or three swallows of the barium suspension are being taken. Displacement or hooklike curvature or angulation of the lower portion of the esophagus is suggestive of hernia and is a common manifestation. Retardation of the barium stream at the hiatus, disparity between the upper level of the gastric contents and the site of the esophageal aperture, or what seems to be a high hourglass deformity should always make the examiner think of hernia. Any deviation from the normal size, contour or general appearance of the lower part of the esophagus or any deviation from its normal relation with the stomach should cause the examiner strongly to suspect hernia and to demand further roentgenoscopic and roentgenographic study with the patient recumbent and strongly tensing his abdominal muscles. This technic is necessary to confirm the presence, and to demonstrate the extent, of herniation. Hernia in which only the colon or small bowel is implicated cannot be confirmed definitely or excluded confidently without employing the barium enema or observing the transit of the barium meal.

The roentgenologic manifestations of diaphragmatic hernia vary with the site of the lesion, the abdominal viscus extruded and the extent of extrusion. These factors in turn are related to other factors, such as the anatomy of the region involved and the cause of the hernia.

As might be expected, many classifications of hernia have been offered, almost as many as there are writers on the subject. Harrington has proposed what seems to me to be the most complete and practicable classification of all, for it can be applied satisfactorily by the surgeon, the clinician and the

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roentgenologist. Items in this classification that are of roentgenologic significance are as follows:

1. Hernia through the esophageal hiatus.
 - a. Congenitally short esophagus with thoracic stomach
 - b. Esophageal hiatal hernia with shortened esophagus
 - c. Esophageal hiatal hernia without shortening of the esophagus
 - d. Para-esophageal hernia through the hiatus.
2. Hernia through the foramen of Morgagni.
3. Pleuroperitoneal hernia.
4. Hernia through congenital defects in the diaphragm
5. Congenital absence of the hemidiaphragm.
6. Posttraumatic hernia.

HERNIAS THROUGH THE ESOPHAGEAL HIATUS

These constitute 98 per cent of the diaphragmatic hernias and are found at more than 1 per cent of all roentgenologic examinations of the stomach at the Mayo Clinic.

Congenitally Short Esophagus with Thoracic Stomach.—This is a rare variety. In this type the esophagus is short and straight and the stomach is not truly herniated, since the supradiaphragmatic portion has never been below the diaphragm. In the single case encountered at the clinic, five sixths of the stomach was above the diaphragm, and the hiatus was 12 cm. in diameter. The roentgenologic diagnosis of hernia should be self-evident in most cases; if the esophagus is extremely short it may fairly be assumed that the condition is congenital, but in less pronounced instances confident distinction from the next variety to be discussed is scarcely possible.

Esophageal Hiatal Hernia with Shortened Esophagus.—This designation is intended to imply that originally the esophagus was of normal length but that it became shortened by tonic contraction following the hernia and that the term "thoracic stomach" does not apply. At operation the surgeon can base this diagnosis on the fact that the esophagus can be stretched to approximately its normal length. Of course the roentgenologist cannot determine whether such elasticity exists or not, but he will incline toward this tentative diagnosis because a large proportion of the hiatal hernias are of this variety, and the true short-esophagus thoracic-stomach variety is exceedingly rare.

Esophageal Hiatal Hernia without Shortening of the Esophagus.—This term is chosen to designate those hernias in which the esophagogastric juncture is above the diaphragm, and the lower end of the esophagus is slightly or markedly redundant, a feature which distinguishes the group from the hernias with shortened esophagus. It is the most common type of hiatal hernia, and 66.5 per cent of the hiatal hernias observed roentgenologically at the clinic in 1944 were of this variety.

Para-esophageal Hernia through the Hiatus.—This term designates a variety of hernia in which a portion of the stomach is extruded through the esophageal hiatus but the esophagogastric junction remains below the diaphragm and the esophagus does not participate in the hernia. Any part of the stomach may be involved but most often the cardia is implicated. The group is small, constituting only 7.5 per cent of the hiatal hernias examined roentgenologically at the clinic in 1944.

In effecting the roentgenologic diagnosis of esophageal hiatal hernia and distinguishing among its varieties, certain items are of fundamental importance. First, the basic point of orientation in the diagnosis is the exact situation of the esophagogastric junction in relation to the diaphragm. Second, retardation of the barium stream at the hiatus is highly significant of hernia, for it occurs in almost all cases. Third, redundancy and tortuosity of the lower portion of the esophagus without dilatation is strongly suggestive of hernia, for it is present in more than one third of the cases.

Many technics have been devised for the demonstration of hiatal hernias. Satisfactory inspection of the esophagogastric juncture and its vicinity can usually be obtained in the customary anterior view with the patient standing. Then as he takes the first swallows of the barium mixture, he should be required to strain his abdominal muscles in order to reproduce any hernia that may have been reduced. Pressure of the examiner's hand over the patient's stomach may also elicit such hernias. If these measures give negative results and doubt persists, roentgenograms should be made with the patient lying on his back and tensing his abdominal muscles.

HERNIA THROUGH THE FORAMEN OF MORGAGNI

This type of hernia, also termed "parasternal" or "costosternal" hernia, is quite uncommon. The so-called foramen is a bilateral, retrosternal, triangular space bounded in front by the sternum, medially by the sternal portion of the diaphragm, and laterally by the costal portion of the diaphragm. The hernia may be unilateral or bilateral, and either stomach or colon, or both, may be implicated. Occasionally omentum only is involved. First evidence of the hernia is likely to consist of abnormal shadows near the midline and at the base of roentgenograms of the thorax. Lateral roentgenograms may reveal fluid and gas in the contents of the hernia, and such findings are strongly suggestive. Examination with the aid of the barium meal, or especially with the aid of the barium enema, since the colon is involved more often than the stomach, may establish the diagnosis.

PLEUROPERITONEAL HERNIA

This type of hernia, or hernia through the foramen of Bochdalek, is a hernia through the posterior segment of the diaphragm, a weak spot and point of fusion in the development of the organ. Those hernias are congenital. Harrington has estimated that 75 per cent of infants with this condition die shortly after birth; few of the remainder reach adulthood. Bizarre shadows in the thorax are likely to be the first clue to the condition, and roentgenologic examination of the stomach, small bowel and colon may lead to the diagnosis.

HERNIA THROUGH CONGENITAL DEFECTS IN THE DIAPHRAGM

These hernias, other than those through the foramen of Morgagni or Bochdalek, have been found most often in infants and children. Usually the hernia is through the left half of the diaphragm, and the stomach, colon, small bowel or spleen may be implicated. Abnormal shadows at the base of the lung, especially on the left, in roentgenograms of the thorax are usually the first observed significant manifestations and call for examination of the alimentary canal with the aid of opaque media.

CONGENITAL ABSENCE OF THE HEMIDIAPHRAGM

Displacement of abdominal viscera into the thorax resulting from congenital absence of a hemidiaphragm is rare. Usually it is the left half of the diaphragm that is wanting. Roentgenograms of the thorax show striking abnormality of the affected side, and the presence of the gas bubble or colonic haustra may indicate that the stomach or colon is in the thoracic cavity. However, administration of the barium meal or enema may be necessary to identify such displacement. In any case distinction of the condition from other varieties of hernia and from eventration is requisite.

An exceedingly rare variety of congenital hernia is that resulting from congenital peritoneopericardial defect with herniation of abdominal viscera into the pericardial sac. Recently a case has been reported by Wilson, Rumel and Ross, who have found only eight similar cases recorded in the literature.

POSTTRAUMATIC HERNIA

Posttraumatic hernia may result from wounds by weapons or missiles, from crushing injury or violent forward flexion of the body, or from localized erosion or inflammatory necrosis of a segment of the diaphragm. Any portion of the diaphragm may be penetrated. Roentgenograms of the thorax constitute a common approach to the discovery and diagnosis of those hernias by disclosing abnormal shadows extending upward from the bases of the lungs. Occasionally the presence of the stomach or colon in the hernia is apparent, but complete and confident diagnosis requires examination with the aid of the opaque meal and enema. If only a solid viscus, such as the liver or the spleen, is implicated, diagnosis may be difficult.

COMMENT

Obviously, the roentgenologic diagnosis of diaphragmatic hernia depends on demonstrating the presence of part or all of an abdominal viscus above the diaphragm, or proving the existence of an aperture in the diaphragm through which an abdominal viscus can be extruded by an increase of the intra-abdominal pressure. In any case the position of the diaphragm must be ascertained by tracing its curvilinear shadow, and this may be difficult in cases of gross traumatic rupture. In an overwhelming preponderance of cases the stomach or bowel participates in the hernia and this fact can be established by administering a radiopaque meal or enema. In all such instances the differential diagnosis is evident. If, however, the hernial content consists of a solid viscus only, such as the spleen or omentum, the lesion is likely to be mistaken for a neoplasm at the base of the lung, although if the hernia is reducible the diagnosis should be evident. Distinction of several varieties of hernia from one another can usually be made. Many hernias will escape discovery unless the roentgenologist keeps the condition in mind at every examination of the thorax and of the alimentary canal.

SYMMETRICAL CALCIFICATION OF THE CEREBRAL BASAL GANGLIA: ITS ROENTGENOLOGIC SIGNIFICANCE IN THE DIAGNOSIS OF PARATHYROID INSUFFICIENCY*

JOHN D. CAMP

In 1939 Eaton, Love and I reported six cases in which symmetric calcification of the cerebral basal ganglia was observed roentgenographically. In two of these cases there was definite clinical evidence of spontaneous parathyroid insufficiency and tetany. In retrospect, our original case, which was reported in 1938 would also seem to be an example of this condition although the diagnosis was not established before death. The basic pathologic changes responsible for symmetric calcification of the cerebral basal ganglia have been noted by many observers since Bamberger's and Virchow's original observations in 1855. However, it was not until 1933 that the first observations concerning the roentgenographic appearance *in vivo* were reported. In that year Fritzsche described the changes observed in roentgenograms of three siblings and Kasamin and Crank described the roentgenographic and the postmortem findings in one case. None of these authors mentioned the presence of parathyroid insufficiency. The older literature contains reports of seven cases of parathyroid insufficiency (tetany) in which calcification of the basal ganglia was observed by pathologists. In most cases the process was marked and roentgenograms would probably have presented the characteristics of symmetric cerebral calcification if they had been made.

To date at the Mayo Clinic we have observed twelve cases of symmetric calcification of the cerebral basal ganglia in which there was definite clinical evidence of parathyroid insufficiency and tetany. In one, the calcification followed a thyroidectomy at the age of nineteen years; in the other eleven, the disease was of the spontaneous type.

The pathologic basis for the roentgenologic changes is one of colloid deposition in and around the finer cerebral blood vessels, with subsequent calcification of the deposits which coalesce and form vascular sheaths and concretions (fig. 113). There is general agreement as to the involvement of the media and adventitia of the smaller arteries and the infrequency with which the veins are affected. When the process is extensive the capillaries may be occluded but the lumens of the arteries are rarely narrowed (fig. 113b). Ostertag concluded that the deposited colloidal material occurs so frequently in the anterior half of the globus pallidus and in the dentate nucleus of the cerebellum that its presence to a slight degree, if not normal, is not unexpected. A marked increase in the degree and extent of the vascular process is likely to occur at any age, in either sex and in response to many diseases, not all of which need produce neurologic symptoms. Calcium is always present microscopically to a considerable degree before it can be revealed by present roentgenologic methods. In five of the twelve cases presented herewith deposits of calcium were observed roentgenographically in the deeper layers of the cerebral cortex as well as in the basal ganglia and cerebellum. The pathologic changes have been most extensive and therefore

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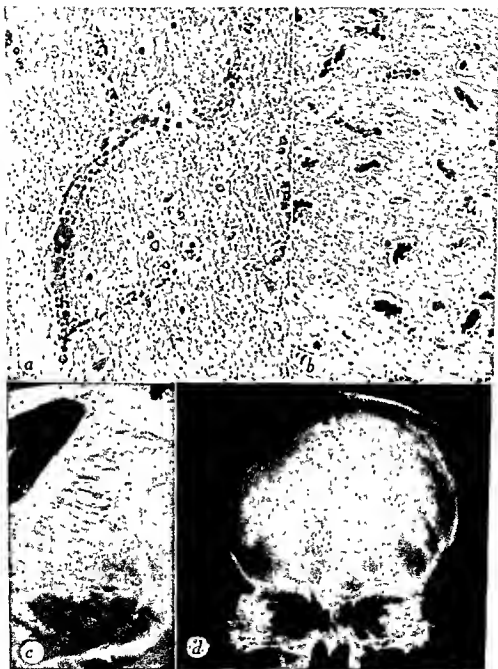


Fig 11 *a*—Histologic changes in the thalamus; pericapillary colloid deposits and calcification ($\times 340$), *b*, mulberry-shaped small concretions with obliteration of capillary lumens ($\times 135$); *c*, gross coronal section revealing calcified nodules of sizes varying up to 3 mm, in their greatest diameter in the lenticular nuclei; *d*, roentgenogram revealing *a*) immetrical distribution and extent of calcification of basal ganglia shown in *a*, *b* and *c*.

are most likely to be detected roentgenologically in parathyroid insufficiency and other diseases characterized by mental deterioration with or without convulsive seizures or motor symptoms referable to the extra-pyramidal system.

Since adequate treatment of parathyroid insufficiency results in a marked improvement of the mental condition of the patient and stops the convulsions without producing roentgenographically detectable changes in the character of the cerebral or cerebellar calcification, it is apparent that the calcification itself is not responsible for the mental deterioration or convulsive phenomena.

SYMPTOMS

The symptoms in general include the various complications of chronic parathyroid insufficiency, namely, cataracts, convulsions, mental retarda-

TABULATION

CLINICAL AND ROENTGENOGRAPHIC DATA IN TWELVE CASES OF
SYMMETRICAL CALCIFICATION OF THE BASAL GANGLIA

Case	Sex	Age, years		Degree of calcification as determined roentgenographically*		
		At onset of symptoms	When observed at the clinic	Basal ganglia	Cerebrum	Cerebellum
1	F	6	27	+++	0	+
2	F	3	15	++	0	0
3	M	19	42	+++	+	+
4	M	42½	44	++	+	++
5	F	6	32	+	0	+
6	M	7½	13	+++	+	0
7	F	39	42	++	+	++
8	F	7	19	+	0	0
9	M	11	19	++	0	0
10	F	2½	2½ 11	0 ++	0 0	0 0
11	F	11½	28	+++	+++	+++
12	F	5	28	+++	0	++

* + = Minimal degree. +++ = Maximal degree.

tion and trophic changes. In three cases the tetany followed an attack of measles. In two of these cases the patients were sisters and the mother

made the diagnosis of parathyroid insufficiency in the case of the younger sister because the symptoms were similar to those observed previously in the older sister. In one case (case 10, tabulation) in which the patient was a girl two and a half years of age, the diagnosis of parathyroid tetany was made at the clinic in 1925. The values for the serum calcium as determined on two occasions at that time were 7.4 mg. and 8.4 mg per 100 c.c. Roentgenographic examination of the skull was reported as negative. The patient had no attacks for one month following treatment and at that time the patient was taken home. Nothing further was heard of her until ten years later (1935), when she was brought back to the clinic because of her mental condition. Inasmuch as the child did not like the medication, it had been discontinued, by the parents, soon after their return home in 1925. When seen ten years later, the child was markedly retarded both mentally and physically, and convulsions were occurring frequently. The values for the serum calcium on two occasions were 6.4 mg. and 6.0 mg. per 100 c.c. The value for the serum phosphorus was 7.2 mg. per 100 c.c. Roentgenograms of the skull revealed symmetrical calcification of the cerebral basal ganglia. Because of her condition, the parents sent the child to a mental hospital for permanent care. It is interesting to speculate on how different the outcome might have been if the original prescribed medication had been continued. It is significant that in none of the twelve cases did a convulsion or "attack" occur after the institution of treatment for parathyroid insufficiency. Mental improvement was marked, and children previously retarded in school were able to keep up with their classmates and some have subsequently gone to college. These facts alone and the possibility of salvaging even a few of the mentally retarded and handicapped persons will justify the search for parathyroid insufficiency in the presence of roentgenographic evidence of symmetrical calcification of the cerebral basal ganglia.

ROENTGENOGRAPHIC FINDINGS

Symmetrical calcification of the cerebral basal ganglia produces a distinctly characteristic roentgenographic appearance (fig. 114a and b). Considerable variation in the degree and extent of this form of calcification may occur, corresponding to the stage of the disease at the time the roentgenographic examination is made. The first roentgenographic evidence of calcification is small, irregular, discrete, symmetrically distributed shadows of increased density in the region of the various basal ganglia, especially the putamen and caudate nucleus (fig. 115). When the calcification is more marked, the irregular shadows take on a wavy linear appearance. This is especially obvious in the dentate nucleus of the cerebellum and in the folds of the cerebellar hemispheres (fig. 116a and b). As the masses of calcium coalesce the roentgenographic shadows become larger, denser and more obvious (fig. 117). Coincident cerebellar calcification may be observed at any stage of the disease as well as evidence of calcification in the deeper layers of the cerebral cortex. The latter may be so marked as to simulate a vascular lesion or calcified glioma.

Roentgenographically, it is important not to mistake the shadows of calcification in the ganglia for evidence of a neoplasm. The fact that the shadows are bilateral and symmetric is usually sufficient to exclude the

possibility of tumor of the brain. If there is any doubt, pneumographic studies may be carried out. With air in the ventricular system the extraventricular position of the calcium shadows and their relation to the site of the basal ganglia will be well shown (fig. 118a and b). In spite of the mental symptoms there was no roentgenographic evidence of other cerebral

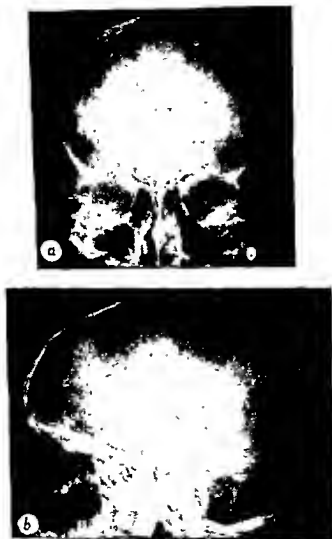


Fig. 114a and b—Characteristic roentgenographic appearance of symmetrical calcification of the cerebral basal ganglia (spontaneous parathyroid insufficiency); a, bilateral symmetrical distribution of shadows of calcification; b, extent of shadows of calcification.

abnormality in the four cases of our series in which pneumographic studies were carried out.

Calcium deposits within the choroid plexus of the lateral ventricles are commonly observed in roentgenograms of normal persons. In certain anteroposterior roentgenograms, the bilateral shadows of calcification of the choroid plexus may simulate calcification of the basal ganglia. However,

when roentgenograms made in the lateral position are examined the distinction between the two conditions should be obvious, since calcification of the choroid plexus is usually limited to the region of the genu of the lateral ventricle whereas calcification of the larger basal ganglia will be

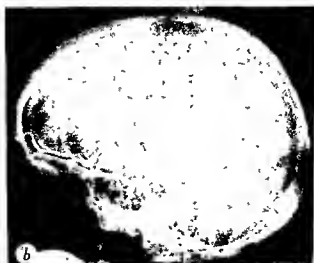


Fig. 115—Minimal calcification in the cerebral basal ganglia, the symmetrical shadows of calcification shown in *a* might easily be mistaken for calcification in the choroid plexus. The shadows of calcification are partially obscured by the density of the overlying shadow of the bone in *b*.

well anterior to this. When calcification of the choroid plexus extends into the temporal horn on each side, it may be difficult to distinguish from calcification in the lentiform nucleus although this seldom occurs without obvious calcification in the putamen and caudate nucleus as well (fig. 119*a* and *b*).

As mentioned previously, calcification of the cerebral basal ganglia is not limited to patients with parathyroid insufficiency. In the course of this study, examples were observed in patients with a previous history of encephalitis, tuberous sclerosis, toxoplasmosis and mental deficiency since

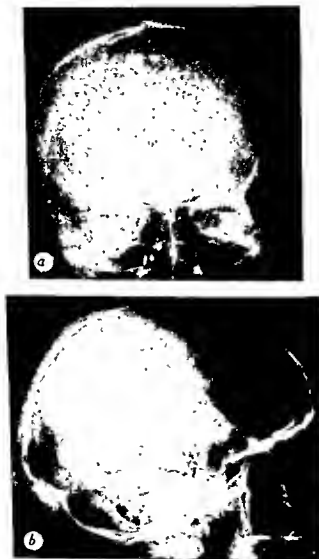


Fig 116a and b.—Roentgenograms revealing extensive calcification of cerebral basal ganglia and cerebellum. There is also bilateral calcification in the cerebral cortex. Spontaneous parathyroid insufficiency.

birth. In one case in which the patient complained only of blepharospasm, there was no obvious cause for the presence of the calcification. In another case in which the calcification was of minimal degree, a mild hyperthyroidism and a positive Kahn test were the only positive clinical findings.

Patients with a previous history of encephalitis and evidence of calcification of the basal ganglia in almost all instances had evidence of other discrete shadows of calcification throughout the cerebrum (fig. 120a and b). This was most obvious in infants in whom the age, abnormalities of the

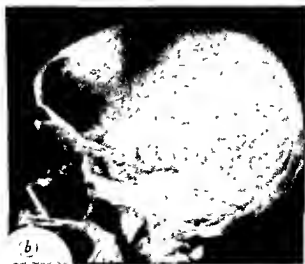


Fig. 117a and b.—Roentgenograms revealing extensive calcification of cerebral basal ganglia. Postoperative parathyroid insufficiency.

calvarium and wide distribution of the shadows of calcification at once suggested a diagnosis other than parathyroid insufficiency.

In tuberous sclerosis, calcification of the basal ganglia when present was always accompanied by nodules of calcification elsewhere in the brain. The latter predominated (fig. 121).

In the presence of toxoplasmosis the calcification in the basal ganglia appears to be very extensive, the calcium occurring in large, dense, irregular masses surpassing any changes observed in parathyroid insufficiency. Calcification of the dentate nucleus is usually very marked and, in addition,

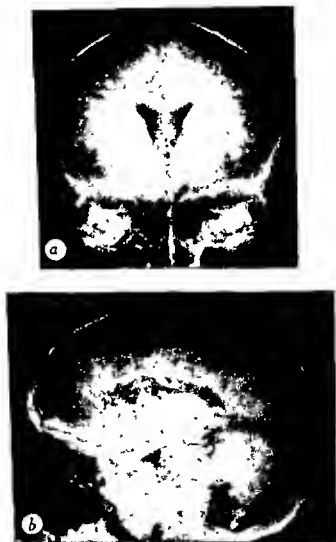


Fig. 118a and b.—Pneumo-encephalograms revealing relation of lateral ventricles to shadows of symmetrical calcification in the cerebral basal ganglia. Spontaneous parathyroid insufficiency. Same case as figure 114a and b

multiple discrete irregular nodules of calcification are distributed throughout the cerebrum (fig. 122). The age of the patient and the evidence of disease at or soon after birth should assist in the proper diagnosis.

Two patients with mental deficiency dating from birth exhibited symmetric calcification of the basal ganglia that could not be distinguished from

that observed in parathyroid insufficiency (fig. 123). There was no clinical evidence of parathyroid dysfunction in either case and the values for the serum calcium and serum phosphorus were normal.

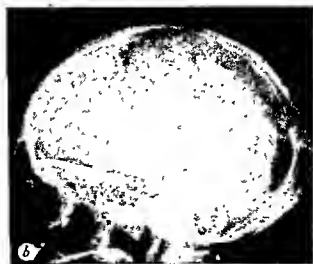
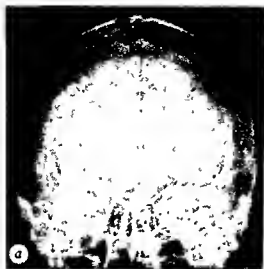


Fig. 119a and b.—Roentgenograms revealing extensive bilateral calcification of the choroid plexus. This may be mistaken for calcification in the lenticular nucleus. Roentgenograms also reveal a plaque of calcification in the falx cerebri.

In the course of this study two patients with unilateral calcification of the basal ganglia of minimal degree were observed. In both cases the calcification was disclosed by roentgenograms made routinely for trivial and unrelated symptoms. There was no evidence whatever of neurologic or parathyroid disease in either case.

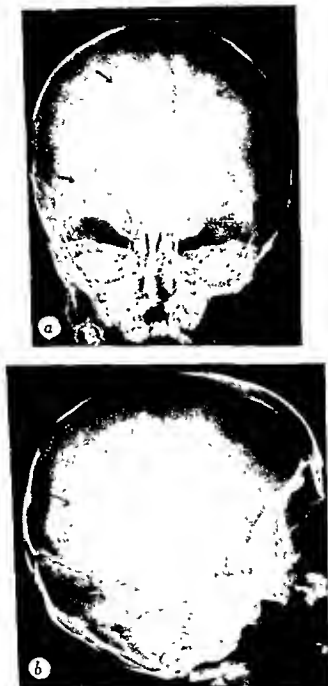


Fig. 120a and b.—Roentgenograms revealing symmetrical calcification of cerebral basal ganglia and extensive calcification in cerebrum. Encephalitis in infancy.

COMMENT

It is evident from this study that parathyroid insufficiency is only one of several diseases producing a disturbance of cerebral metabolism which

results in the deposition of colloid material in and about the finer cerebral vessels with subsequent calcification. The basal ganglia and dentate nucleus have long been recognized by pathologists as common sites of

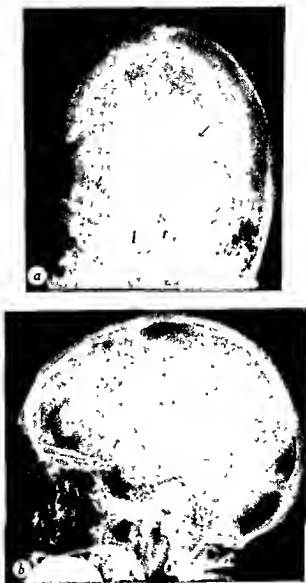


Fig. 121a and b.—Roentgenograms revealing symmetrical calcification of cerebral basal ganglia. There are also nodules of calcification elsewhere in the cerebrum and massive calcification in the right lobe of the cerebellum. Tuberosus sclerosis.

predilection for the process. Because of the rarity of spontaneous parathyroid insufficiency and the observance of eleven such cases in which symmetric calcification of the cerebral basal ganglia was observed, I

believe the association of the two conditions should be emphasized. It is possible that some cases of marked cerebral calcification associated with mental deterioration and convulsive seizures reported in the literature may



Fig. 122a and b.—Roentgenograms revealing irregular nodular masses of calcium more or less symmetrically distributed in cerebrum, basal ganglia and dentate nuclei of cerebellum. Toxoplasmosis in infancy. Identical twin brother had same condition.

have included a parathyroid insufficiency which was not detected. For this reason, the skull of all patients with chronic parathyroid insufficiency should be examined roentgenographically. In addition, a determination of

the concentration of serum calcium should be made to establish or exclude parathyroid insufficiency in all cases in which roentgenograms show symmetrical calcification of the cerebral basal ganglia. The prompt response to

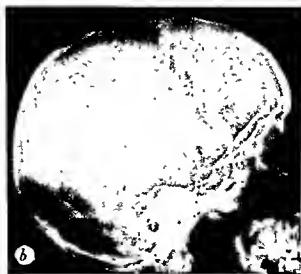
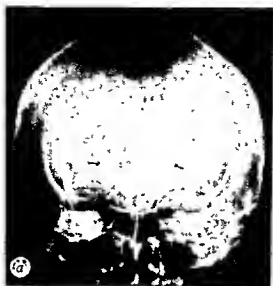


Fig 143a and b.—Roentgenograms revealing symmetrical calcification of the cerebral basal ganglia. Mental deficiency since birth, no clinical evidence of parathyroid insufficiency.

adequate treatment in such cases and the possibility thereby of salvaging an occasional mentally retarded or handicapped person or child should adequately justify our endeavors.

THE IMPORTANCE OF FOLLOW-UP ROENTGENOGRAMS IN PULMONARY DISEASE*

C. ALLEN GOOD

It has long been recognized that follow-up roentgenograms are necessary in watching the course of pulmonary tuberculosis. Progression or regression of the disease cannot be ascertained from a single roentgenographic examination. To state definitely that a tuberculous lesion is active almost always requires serial examinations or the demonstration of a cavity.

It is also recognized that periodic roentgenographic examinations are necessary when dealing with a patient who has a solitary, well-circumscribed tumor in a lung. In such cases, exploration is advisable when on succeeding roentgenograms the tumor shows signs of growth.

It remains for physicians to be aware also of the necessity for follow-up roentgenograms when treating a patient whose clinical course is that usually associated with pneumonia. Any lesion which obstructs a bronchus, whether it be a carcinoma, a foreign body, a pulmonary cyst, a broncholith or an inflammatory stricture, may cause symptoms which simulate those encountered at the onset of pneumonia; so may the inflammatory processes which accompany bronchiectasis or pulmonary abscess. Improvement may be noted both in the condition of the patient and in the roentgenologic appearance of the lung following treatment with one of the antibacterial drugs. Nevertheless, the underlying lesion will still be present and the roentgenographic appearance of the lung will not be normal. Only when the roentgenographic appearance of the lung has returned to normal can the physician forget the possibility that his patient may be suffering from one of the complications of pneumonia, or from some other possibly more serious lesion.

THE ROENTGENOLOGIC EXAMINATION OF THE SMALL INTESTINE†

C. ALLEN GOOD AND M. ELIZABETH H. FLETCHER

Examination of the small intestine, if properly done, is one of the most difficult and time-consuming tasks which confronts the roentgenologist. It demands frequent roentgenoscopic observations during which an attempt is made to visualize and palpate every segment of the barium-filled bowel. In most cases three to eight periods of roentgenoscopy are required to examine the entire small intestine after the oral administration of opaque material. Lesions which are encountered must be recorded on roentgenograms often by means of "spot" roentgenography, and this adds to the

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difficulty of the task. In addition, the diseases which involve this segment of the digestive tract are relatively rare. The examination should not be used as a routine procedure. Instead, patients who are to be referred to the roentgenologist for investigation of the small intestine should be selected with great care.

In order to aid in the proper selection of such patients, the clinical manifestations of the more common lesions of the small intestine will be discussed, the frequency with which these lesions are encountered will be commented on, and the accuracy with which they may be found and identified by the roentgenologist will be noted.

ENTERITIS

Nonspecific regional enteritis is the most common inflammatory lesion of the small intestine. During the period between January 1, 1942, and January 1, 1946, fifty-three patients who suffered from this disease were operated on for the first time at the Mayo Clinic. Excluded from consideration for the purposes of this discussion are all patients who were subjected to a secondary type of operative procedure and all patients on whom no operation was performed.

TABLE 1

CLINICAL MANIFESTATIONS IN FIFTY-THREE CASES OF NONSPECIFIC ENTERITIS

Clinical manifestations	Cases	
	Number	Per cent
Loose or watery stools	39	74
Cramping abdominal pain . .	36	68
Loss of more than 10 pounds in weight	39	74
Anemia or loss of blood in stool	20	38
Palpable mass in abdomen .	15	28
Fever.	9	17
Partial or complete obstruction . . .	7	13
Fecal fistula	4	8

The chief clinical manifestations of nonspecific regional enteritis as noted in this group of cases are listed in table 1. It will be seen that the passage of loose or watery stools, cramping abdominal pain and loss of weight were the most common expressions of this condition. Cramping pain or loose stools, or both, were present in all but three of the fifty-three cases.

An adequate roentgenologic examination of the segment of bowel which was involved was not obtained in five of the fifty-three cases. Of the forty-eight cases in which adequate roentgenologic examination was obtained a

diagnosis of regional enteritis was made in forty-five and of obstruction of the small intestine in one. In the two remaining cases, the diagnosis was erroneous, although a lesion was found. A correct diagnosis, therefore, was made in 95.8 per cent of the cases in this group.

Regional enteritis involves the terminal portion of the ileum most commonly but it may implicate any portion of the small intestine. In four of the fifty-three cases in this group the jejunum was involved. In many instances the lesion extended beyond the ileocecal valve to involve the cecum and a portion of the ascending colon.

Enteritis due to tuberculosis has not been encountered frequently in our experience. It is difficult roentgenologically to distinguish this lesion from the nonspecific variety. The presence of an extra-alimentary focus of tuberculosis lends weight to a diagnosis of tuberculous enteritis when a lesion is found in the small intestine.

TUMORS

During the seven years from January 1, 1939, to December 31, 1945, inclusive, sixty-one patients were subjected to operation at the Mayo Clinic because of a tumor in the small intestine. The thirty-five cases

TABLE 2

TUMORS OF SMALL INTESTINE ENCOUNTERED FROM 1939 TO 1945, INCLUSIVE

Type of tumor	Cases		
	1929-1941, inclusive	1942-1945, inclusive	Total
Adenocarcinoma	16	10	26
Carcinoma, carcinoma type	3	1	4
Miscellaneous malignant lesions	2	1	3
Lymphoblastoma	1	5	6
Adenoma	1	1	2
Leiomyoma (includes leiomyosarcoma)	6	4	10
Lipoma	3	2	5
Polyp, unclassified	0	1	1
Cyst, mesenteric	2	1	3
Extrinsic tumor, unclassified	1	0	1
Total	33	26	61

encountered during the first three years of this period have been reported before. The pathologic types of tumor which were seen and the frequency of their occurrence are listed in table 2. Eight of these lesions involved the

duodenum, thirty-four the jejunum, and nineteen the ileum. Twenty-two of the carcinomas and eight of the leiomyomas were situated in the upper portion of the small intestine.

The most important clinical manifestations in this group of sixty-one patients were (1) evidence of loss of blood, (2) presence of a mass in the abdomen and (3) evidence of partial intestinal obstruction. The incidence of these features, alone and in combination, is given in table 3. The passage of tarry or bloody stools, hematemesis or a value of hemoglobin of less than 12 gm. in 100 c.c. of blood are included in the group listed as "loss of blood." In the five instances in which the only indication of the tumor was a

TABLE 3

CLINICAL MANIFESTATIONS IN SIXTY-ONE CASES OF TUMORS OF THE SMALL INTESTINE

Clinical manifestation	Cases		
	1939-1941, inclusive	1942-1945, inclusive	Total
Loss of blood* only	10	11	21
Loss of blood* and mass	8	1	9
Loss of blood,* mass and obstruction	1	1	2
Loss of blood* and obstruction	4	4	8
Mass alone	3	1	4
Mass and obstruction	2	4	6
Obstruction alone	2	4	6
No manifestations	2	0	2
Total	35	26	61

* Includes also cases of secondary anemia in which other evidence of loss of blood was not found.

low value of hemoglobin, the highest value was 8.9 gm. and the lowest was 5.5 gm. in 100 c.c. of blood.

The most common clinical manifestation of a benign tumor was evidence of loss of blood while that of lymphoblastoma was evidence of intestinal obstruction. In the group of cases which included carcinoma and certain other malignant tumors the manifestations of loss of blood and of obstruction were noted with equal frequency.

Nineteen of the sixty-one patients who were operated on had not had complete roentgenologic examination of the small intestine. In five of these cases a diagnosis of intestinal obstruction was made from roentgenograms of the abdomen without the use of a contrast material. Evidence of intestinal obstruction or of an abdominal mass was present in thirteen of the other

fourteen cases. In one case exploration was carried out because of a massive hemorrhage from the gastro-intestinal tract.

In the forty-two cases in which adequate roentgenologic examination of the small intestine had been done, the lesion was demonstrated at the time of this examination in thirty-six and overlooked in six. A correct roentgenologic diagnosis was made in 85.7 per cent of the cases in this group.

Tumors of the small intestine usually are manifest in one of three ways; namely, (1) by producing obstruction, (2) by causing intussusception and (3) by producing a filling defect in the column of opaque material. Only in the last-mentioned instance is it possible for the roentgenologist to obtain sufficient information so that he can attempt to make a definite pathologic diagnosis. For this reason the following diagnoses were made by the roentgenologist in the thirty-six cases in which the tumor was found roentgenologically: carcinoma in ten cases; ulcerating malignant lesion in three cases; intramural submucosal tumor in seven cases; intraluminal polypoid lesion in three cases; intussusception in five cases; obstruction in six cases and lesion in two cases.

MECKEL'S DIVERTICULUM

Dixon, Deuterman and Weber stated that approximately 25 per cent of the acquired diverticula of the intestines are found in the small intestine. In 18 per cent of cases of diverticula of the intestine the lesions are situated in the duodenum and these almost never produce symptoms. Those which are situated in the jejunum and ileum are rare and seldom produce symptoms. Much more important to the roentgenologist and the clinician is Meckel's diverticulum which is present in about 2 per cent of all individuals. It is twice as common in males as in females.

Clinical Manifestations.—The clinical manifestations of this type of diverticulum can be divided into six distinct groups, as follows:

Peptic.—Meckel's diverticulum is frequently the site of heterotopic tissue, most commonly gastric mucosa. As it does in the stomach and duodenum, the acid secretion of this tissue may produce a peptic ulcer. This ulcer may be situated in the diverticulum or in the ileum near the diverticulum. The most common symptom produced by this type of lesion is hemorrhage.

Obstructive.—Meckel's diverticulum may become inverted and push into the lumen of the ileum. When this happens, intussusception may take place and cause intestinal obstruction. Obstruction also may be brought about by congenital bands or acquired adhesions attached to the diverticulum or by perforation of the diverticulum.

Inflammatory.—When inflammation occurs in a Meckel's diverticulum, the symptoms are like those commonly associated with a similar lesion of the vermiform appendix.

Umbilical.—A cutaneous umbilical fistula may be present. Patients who have this type of lesion are seldom referred for roentgenologic examination of the small intestine.

Neoplastic.—Meckel's diverticulum may be the site of a benign or malignant neoplasm. Many pathologic types have been described. In cases of this sort the lesion may exist without symptoms or bleeding, pain, mass or obstruction may occur.

Incidental.—Most Meckel's diverticula show no evidence of a pathologic process and consequently produce no symptoms. They may be discovered as an incidental finding at operation or at roentgenologic examination.

Clinic Series.—During the period from January 1, 1942, to December 31, 1945, inclusive, seventeen patients were operated on at the Mayo Clinic because of a definite pathologic process associated with Meckel's diverticulum. There were eleven males and six females. Fourteen of these seventeen patients gave a history of hemorrhage from the bowel, with the passage of tarry stools, plum-colored or bright red blood. Four of these fourteen patients also had experienced pain in the abdomen. One patient, in addition to these fourteen, had suffered from severe anemia for twelve years but gave no history of passing blood in the stool. In all but one of these fifteen cases, the pathologist found gastric mucosa to be present in the diverticulum. In the one exception intussusception had been demonstrated roentgenologically and this process probably accounted for the bleeding.

Two of the seventeen patients gave no history or had no symptoms referable to loss of blood. One of these patients, who suffered from attacks of partial intestinal obstruction, was found at the time of operation to have adhesions around the diverticulum. These had produced obstruction of the ileum. The other patient had experienced attacks of pain in the abdomen. He was found to have an inflamed and perforated diverticulum. Gastric mucosa was present in the diverticulum removed from this patient.

An adequate roentgenologic examination of that portion of the small intestine bearing the diverticulum was obtained in eleven of the seventeen cases of Meckel's diverticulum. The diverticulum was overlooked in five instances and a lesion was found in six. In one case the diagnosis was that of obstruction. In one case a constricting lesion was seen and Meckel's diverticulum was one of the possibilities mentioned in the roentgenologist's report. In four instances the Meckel's diverticulum was identified.

Meckel's diverticulum is the lesion of the small intestine most likely to be overlooked by the roentgenologist. The anomaly is known to be present in about 2 per cent of all individuals, and yet Weber and Good were able to collect from their experience and from a review of the literature less than fifty cases in which the diverticular sac was identified by roentgenologic methods. The usefulness of the roentgenologic examination of the small intestine in a case of suspected Meckel's diverticulum rests, therefore, on the ability of the method to exclude other lesions which might produce the symptoms of which the patient complains rather than on its capacity for visualizing the diverticulum. Of course, when the diverticular sac is seen the diagnosis is obvious.

COMMENT

In our experience the lesions most frequently encountered in the small intestine during roentgenologic examination have been nonspecific regional enteritis, neoplasm, both benign and malignant, and Meckel's diverticulum. These lesions caused four distinct types of clinical manifestations. The first type was a syndrome of loose or watery stools, cramping abdominal pain and loss of weight. This symptom complex was seldom caused, in the group of cases studied, by a lesion other than enteritis. The second type of clinical manifestations was characterized by various forms of gastro-

intestinal bleeding. The loss of blood was indicated by the passage of tarry stools, the passage of bright red or plum-colored blood in the stools, the presence of occult blood in the feces or the presence of an anemia of the secondary or blood-loss type. The lesions in the group of cases studied which most frequently caused this type of clinical manifestation were the tumors and Meckel's diverticulum. Intestinal obstruction constituted the third type of clinical manifestation. This was encountered more frequently in cases of neoplasm, but it also was seen in cases of enteritis and Meckel's diverticulum. The final type of clinical manifestation was the presence of a mass in the abdomen. Such a mass was found in cases of neoplasm and in cases of enteritis.

Roentgenologic examination of the small intestine should not be undertaken until it has been proved that there is no lesion in the colon, stomach, or first portion of the duodenum which might account for the symptoms of the patient. This is especially true when the purpose of the examination is to search for a cause of bleeding from the gastro-intestinal tract.

No patient suffering from acute intestinal obstruction should be referred for roentgenologic examination of the small intestine. This type of patient either should undergo immediate surgical exploration of the abdomen or should receive treatment which is directed toward relieving the obstruction.

The diagnostic accuracy of the roentgenologic examination of the small intestine in the types of lesions discussed is highest in cases of regional enteritis, fairly high in cases of benign and malignant tumor, and lowest in cases of Meckel's diverticulum. Although the examination probably never will yield the high percentage of accurate diagnoses attained from the roentgenologic examinations of the stomach and colon, nevertheless, when properly done, the diagnostic yield is sufficiently large to warrant its use whenever a lesion of the small intestine is suspected.

INTRACAVITARY RADIUM THERAPY FOR CARCINOMA OF THE UTERINE CERVIX*

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In the main, intracavitary radium therapy may be defined as the application of radium to the surface of a lesion occurring in any hollow place or space. It not only is the oldest method of radium therapy of carcinoma of the uterine cervix but it also is a conservative method. Many improvements and refinements have made the method most effective. Our experience with this method at the Mayo Clinic covers a period of thirty years. During this time, the technic employed has been rather constant, which permits the widest possible interpretation of the variable factors inherent in the patient and the disease.

The history, bimanual palpation, inspection and sounding of the genital tract, especially in the predominating stage 3 lesion, are essential for

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diagnosis and treatment. A general physical examination and the required laboratory tests, including the removal of tissue from the primary lesion for microscopic study, are absolutely essential from the standpoint of good management. A knowledge of pathology and physiology will sharpen the interest of the therapeutic radiologist. As a rule, constant vigilance by the physician and patient will be an important element in obtaining a good immediate and late result.

The standard platinum tube containing 50 mg. of radium sulfate (element) is used; the walls of the tube are 1 mm. thick. The applicator may contain one or more tubes. When distance is employed, it is maintained with 2 mm. or 1 cm. of Para rubber. The following factors are approximate for treatment of the average stage 3 lesion. The time of the application may vary from three to twenty-four hours; the dose, therefore, varies from 300 to 2,400 milligram hours. The interval between applications may vary from one to seven days. The total time consumed may be ten to twenty-one days. The treatment area is divided into zones and the dose in milligram hours applied to each zone is as follows: to the vaginal zone 2,100, to the proximal cervical zone 1,400, to the distal cervical zone 1,400 and to the intra-uterine zone 2,000 to 2,400.

The method requires hospitalization only for the day of the treatment. The time that the patient has to spend in the hospital may vary from eight to ten days. No general anesthetic is used. A dose of $\frac{1}{2}$ grain (0.01 gm.) of morphine sulfate may be administered hypodermically before the treatment. Barbiturates are used sparingly. All other drugs are given by the physician on the medical hospital service. In the past few years, the field has been dusted with a sulfonamide drug at the same time that radium therapy is applied. All applications of radium are made with the patient in the knee-chest position. With gentle unilateral separation of the labia, air is admitted to the vagina, which permits a type of endoscopic examination. The endoscope consists of a Sims speculum and a direct electric lamp with a suitable handle. The vagina becomes a distended hollow organ and permits: (1) visual and palpatory examination of the normal and pathologic tissues; (2) selection of the site for the removal of representative material for biopsy; (3) the location of anatomic landmarks; (4) the placement of the radium applicator, and (5) the placement of gauze packing to hold the applicator in position and to obtain as much distance as possible between the applicator and the adjacent normal anatomic structures. As the treatment proceeds, the gross changes occurring in the neoplastic tissue owing to the rays of radium are readily visualized and their distribution and intensity guide the radium therapist in his treatment of the lesion. All procedures are carried out with a minimum of trauma.

In some cases, the cervical canal is eccentric to the main malignant tumor. In this event, the applicator is placed in the center of the malignant medullary mass. In cases in which the mass is very firm, a slight stab wound may have to be made for the applicator.

As a rule, no anatomic difficulties are encountered in cases in which the lesions are classified as stage 1 or 2. The applications of radium may be carried out daily so long as no distressing systemic effects occur. However, lesions which are classified as stage 3 or 4 may distort the anatomic landmarks and make their identification tedious and in some cases impossible.

at the first treatment. A large medullary cervical mass or a large crater with necrotic walls is the chief offender in this regard; however, as time passes, these features of the malignant process are resolved, the field is restored to a more normal state and radium can be applied throughout the involved region. Distribution of the radium is an essential element in the intensive broken-dose method. Although the individual response to treatment will vary, it can, in a measure, be anticipated.

Judgment and skill are necessary for the greatest individualization of the intracavitary method of treatment. The response should occur rather slowly instead of a rapid change which may result in necrosis and distressing complications, such as a persistent discharge, foul odor, hemorrhage and fistulas.

Judgment is necessary in selecting and outlining the type of radium treatment at the time of the first consultation. The outline should be designed for cure or palliation. To be sure, the total treatment time will furnish data that may alter the first estimation. In this event, the alteration should be fully discussed with the staff and, if accepted, should be charged against the judgment of the radium therapist. Provided all zones can be treated as outlined, the procedure is classified as a complete treatment designed for cure; otherwise, it is classified as a limited treatment designed for palliation. On subsequent visits, the complete radium treatment should not be repeated; however, limited radium treatments may be applied to sites of active involvement in order to extend the period of palliation.

SUPPLEMENTAL ROENTGEN THERAPY

Roentgen therapy is started a few days before radium therapy is completed. The pelvis is divided into two anterior and two posterior fields. The roentgen rays are generated at 200 kv.* and are filtered with approximately 0.75 mm. of copper and 1 mm. of aluminum. A dose of 500 to 700 r is applied to each field. In selected cases, the doses are divided and 250 to 350 r are administered daily. In cases in which the patients are very obese, additional filtration is used to obtain better penetration of the rays but the dose per field is about the same as that employed in the average case. The doses are measured in air. In the average case in which the lesion is classified as stage 3, a second course of roentgen therapy usually is given after an interval of three months. We do not use larger doses of roentgen rays because they are likely to cause irritation of the bladder or intestine. The irritation of the intestine may cause bleeding from the mucous membrane and eventually may produce scarring and obstruction.

Roentgen therapy was employed alone in forty-one of a series of 1,491 cases in which irradiation therapy was used in the years 1915 to 1929, inclusive. In cases in which roentgen therapy is employed without radium therapy, the roentgenologic technique is the same as that which has been described, with the exception that the doses applied to each field may be increased to approximately 1,000 r.

RESULTS

The early response to treatment is most gratifying. The first response observed is the control of bleeding, which may occur in two or more days.

* Prior to 1921, we used roentgen rays generated at 155 kv.

The distressing unilateral aching in the back, hips and legs may respond in four or five days. The discharge and odor of the lesion are the last features to respond to treatment.

The patients are instructed to return for examination every three or four months, during the first year after irradiation treatment, every six or nine months during the second and third years, and every year thereafter.

The following analysis of the results of treatment is based on 1,491 cases in which this type of treatment was employed at the clinic in the years 1915 to 1929, inclusive. As previously stated, roentgen therapy was the only type of treatment employed in forty-one of these cases. In fifteen, or approximately 1 per cent, of the cases, the patients died while they were in the hospital.

As the patients returned during the first year after their treatment, the late response was found to be equally gratifying. The uterine and adnexal infiltration was markedly reduced in extent. In some cases, the pelvic structures were free of any palpable characteristic infiltration due to residual malignant activity. As the years passed, statistical data were available to confirm our initial clinical impressions. During the first five years of our experience with this type of treatment, that is, in the years 1915 to 1919, inclusive, the treatment was used in 288 cases. Follow-up data were obtained in 264 of these cases. Of the 264 traced patients, thirty-eight, or 14.4 per cent, were living three or more years after the completion of treatment. During the years 1920 to 1924, inclusive, the treatment was used in 556 cases. Follow-up data were obtained in 522 of these cases. Of the 522 traced patients, 185, or 35.4 per cent, were living three or more years after the completion of treatment. During the years 1925 to 1929, inclusive, the treatment was used in 647 cases. Follow-up data were obtained in 585 of these cases. Of the 585 traced patients, 250, or 42.7 per cent, were living three or more years after the completion of treatment. In several of the cases in each of these groups, the lesions had been modified by treatment before the patients came to the clinic.

This rather definite increase in the percentage of patients who lived three or more years after the completion of treatment was due to several factors, including (1) a satisfactory method of vaginal endoscopy to facilitate the placement of the applicator and gauze packing with minimal trauma; (2) the observation of the vaginal field during the initial days of therapy to guide the selection of the most effective treatment factors for each patient; (3) better distribution of the radium applicators in the vaginal and uterine fields of involvement, and (4) the early recognition and treatment of potential and actual complications, such as bleeding and serious hemorrhage, localized inflammation and necrosis of tissue.

In 1,079 of the 1,491 cases, the lesions had not been modified by previous treatment. In these cases the lesions were classified as follows: stage 1 in thirteen cases, stage 2 in eighty-five cases, stage 3 in 825 cases and stage 4 in 156 cases. Follow-up data were obtained in all of the cases in which the lesion was classified as stage 1. Nine, or 69.2 per cent, of the thirteen patients were living five or more years after the completion of treatment. Follow-up data were obtained in seventy-eight of the eighty-five cases in which the lesion was classified as stage 2. Of the traced patients, forty-seven, or 60.2 per cent, were living five or more years after the completion of

treatment. Follow-up data were obtained in 753 of the 825 cases in which the lesion was classified as stage 3. Of the 753 traced patients, 224, or 29.7 per cent, were living five or more years after the completion of treatment. Follow-up data were obtained in 138 of the 156 cases in which the lesion was classified as stage 4. Of the 138 traced patients, nine, or 6.5 per cent, were living five or more years after the completion of treatment.

The type of radium therapy employed has a definite effect on the prognosis. Of 565 traced patients who received a complete course of radium therapy, 209, or 37.0 per cent, lived three or more years after the completion of treatment, of 739 traced patients who received a limited course of radium therapy, only 158, or 21.4 per cent, lived for three or more years.

COMMENT

Evidently therapeutic radiologic judgment is an important element in prognosis since it possibly may increase the chance of survival for three years or more. All supplemental efforts should be employed to further the possibility of applying a *complete* course of treatment. However, as a word of caution, we must not overtreat a very advanced lesion and in this way bring about distressing features to add to an already overburdened and apparently seriously ill patient. No data are available for an estimation of the morbidity rate in this series of cases. Morbidity occurred, however, but we were not impressed by the number and severity of the reactions.

Today the responsibility of the therapeutic radiologist in the treatment of carcinoma of the uterine cervix is very great. The patient and her restoration to health as a possibility should be the major concern.

The outline of a plan of radiation treatment made at the initial consultation and designed for cure or palliation and to meet the therapeutic requirements of the patient will produce the best results.

The radium technic must be very flexible. For example, it must be adaptable to the therapeutic requirements of the stage 1 and stage 2 lesions, notwithstanding the fact that they are few in number when compared with the stage 3 and stage 4 lesions, as well as the recurring and modified lesions and their usual distressing complications. The radiologist's comprehension and knowledge will guide him in the selection of the most effective treatment factors.

There is no substitute for patience and an allotted time in determining the most effective therapeutic strategy. Interest in the patient's recovery must extend through the initial period of treatment and the months and years that follow. With judicious, skillfully applied intracavitary radium therapy as the initial treatment, supplemented by roentgen therapy, it is possible to influence favorably the discharge, odor, pain, bleeding and the potential distressing sequelae, such as fistulas, unilateral edema of the extremities and hydronephrosis. In some cases, sound permanent healing of the primary lesion will occur in a minimal treatment time with a low mortality and morbidity rate. There should be no conflict between radium therapy and roentgen therapy; I contend they should be employed to complement each other; the greater the co-operation and co-ordination of effort, the more effective will be the treatment.

There are few data in the therapeutic radiologist's field of endeavor that will furnish material for generalization; instead, the patient and the disease

are both characteristically individual, as well as the response to treatment. However, in a measure, a certain pattern of satisfactory response will be observed, and yet it cannot be definitely predicted.

With an enlightened womanhood, an alert physician and a skillful specialist, guided by sound therapeutic judgment, the initial result should be prompt and the late result should be more permanent, or the period of palliation should be longer and more enduring.

SUMMARY

Briefly stated, the intracavitary, intensive broken-dose method of radium treatment, followed by supplemental roentgen therapy, furnishes a wide range of individualization for the greatest number of patients who have carcinoma of the uterine cervix. The treatments can be designed for cure or palliation. The immediate subjective and objective response occurs rather promptly. As time passed, favorable statistical data were available to support our initial interest and to encourage us to improve and refine this conservative method of radium treatment for carcinoma of the uterine cervix.

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PEYRONIE'S DISEASE AND ITS TREATMENT WITH RADIUM*

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Cabot has called Peyronie's disease one of the more common rare diseases of the penis. Since its original description by Peyronie in 1743 it has been described under a variety of names: fibrous plaque of the penis, fibrous cavernositis, chronic cavernositis, fibrous sclerosis and plastic induration of the penis. The tunics of the corpora cavernosa or the intercavernous septum or both are involved in induration which may result in formation of a plaque, nodule, cord or band, readily palpable and superficial, although not attached to the overlying skin. The corpus spongiosum and urethra are not involved. On erection the presence of this plaque or band causes an abnormal bending of the penis, usually without pain, although pain may be present. This bending becomes extreme and eventually may prevent sexual intercourse altogether. Plaques have been excised for microscopic study. They exhibit bundles of collagen fibers with fibroblasts between them, a few blood vessels and not many elastic fibrils; in other words, they seem to resemble a keloid. Eventually, in long-standing untreated plaques, calcium and bone may be formed.

The etiology of fibrous plaques is unknown. A variety of chronic conditions have been cited as causative factors, but no positive proof has been forthcoming. Many urologists believe the condition is due to trauma, even though a history of trauma rarely is elicited; the belief probably is justified because of the resemblance of the lesion to keloids on microscopic examination.

Treatment has been varied and not too successful, as can be guessed

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because many agents are employed. Johnson listed as therapeutic measures topical applications of iodine, mercury, camphor, iodoform and such drugs; internal use of iodides and arsenical drugs; injection of fibrolysin and use of electrolysis, faradic current, ultraviolet rays, short wave diathermy, excision, roentgen therapy and radium treatment.

The lesion occurs in patients of any adult age, but the majority of patients are more than fifty years of age. It is found in patients of all walks of life. The diagnosis readily is made by considering the history, the symptoms and the characteristic physical findings. Formerly, it was considered a rare disease; in 1928 Polkey found 549 cases in the literature and added another. By 1940 Burford found that forty more cases had been reported and added forty of his own, a total of 630.

In 1939, thirty-four cases in which radium was used for treatment at the Mayo Clinic during three preceding years were reported. Of the thirty-one patients traced, 48.3 per cent were unimproved by the treatment, but the remainder had good or fair results. We have continued to treat this disease with radium since then in increasing numbers of cases. Many inquiries from other physicians and their interest in the problem have prompted us to review our experience with treatment of the condition with radium at the clinic from 1938 to 1943, inclusive.

TREATMENT

Physicians favor varied types of treatment. Cabot mentioned roentgen treatment or excision, as does Polkey. Johnson preferred surgical excision, but stated that recurrences are common. Corbus favored use of diathermy. Burford, Soiland and others believed that radium therapy achieved the best results.

Technic.—At the Mayo Clinic, our own preference in the treatment of this disease has been radium therapy. We have used heavily filtered radium, at a distance from the skin, over the entire shaft of the penis. To gain extension of the organ, the ends of a loop of adhesive tape are fastened to the sides of the penis; a rubber band through the center of the loop is attached to the leg just above the knee with adhesive tape, thus exerting traction. A lead plate is placed over the scrotum, as protection for the scrotum and as a support for the balsa wood blocks carrying the radium tubes. On a flap of transparent cellophane the upper margin of which is taped to the lower part of the abdomen are placed the three wooden blocks (each block has a base measuring 3 by 3 cm.) and each of the blocks is surmounted by a 50 mg. radium tube filtered with 1 mm. platinum. The blocks are 1 inch (2.5 cm.) in height and cover the full length of the extended penis. To the undersurface of the cellophane flap wooden blocks are taped, one on either side of the penis, as a support. The radium is left in place for twelve hours. The patient lies flat on his back; the head of the bed is elevated so he can read and keep awake during the treatment. When it is necessary to use a urinal, the patient can undo the rubber band around the loop of adhesive tape, raise the cellophane flap, void and replace the apparatus himself. The supporting wooden blocks on the undersurface of the flap, one on either side of the penis, serve as guides in replacement. The dose, three 50 mg. tubes at 1 inch distance, spaced as described, for 12 hours is suberythema.

The main features of treatment are: (a) by extending the penis by traction, the whole shaft is treated adequately and (b) by placing radium at a distance, injury to the normal tissues can be avoided. Neither erythema nor distressing edema has occurred in any case.

Treatments are spaced three months apart. If no apparent benefit followed treatment, we usually stopped our efforts after the third application. Sometimes a patient was helped sufficiently by only one or two applications, so that no more treatment was needed.

Results.—During the six year period from 1938 to 1943, inclusive, 141 patients were treated with radium at the Mayo Clinic for fibrous plaque. This was an average of approximately twenty-four patients a year. The two youngest patients were twenty-seven years old and the two oldest, seventy years old. The average age was 53.2 years.

One treatment only was given to eighty-six patients. Six patients had four treatments each. The average number of treatments per patient was 1.5.

Information concerning results of treatment was obtained by re-examination of patients or by letters from patients or from their physicians elsewhere. We were able to determine results in 112, or 79.4 per cent of the total. Our study is based on findings in these 112 cases.

We judged the results rather critically and demanded evidence of decided improvement before classifying a result as good. We found a poor result (no improvement discernible whatever) in fifty cases or 44.6 per cent. A fair result (some definite benefit) was obtained in twenty cases or 17.8 per cent. A good result was noted in twenty-eight cases or 25 per cent and an excellent result or cure in fourteen cases or 12.5 per cent.

We thought that perhaps the age of the patient, the duration of symptoms before treatment was instituted or the number of treatments might be important factors in the result of treatment. The study of thirty-one traced patients reported by Olds and one of us in 1939 indicated that the patients not benefited by treatment had had the disease much longer before treatment was started and also had had fewer treatments. However, in this study of 112 traced patients, there seems to be no essential difference in results of treatment because of the patient's age, duration of symptoms or number of treatments given.

SUMMARY

Fibrous plaque of the penis disturbs no vital function and is not a serious condition; however, the disease tends to cause severe mental distress and every effort should be made to cure the condition. The disease occurs usually in middle-aged patients. It appears to be a self-limiting process. Although formerly this was considered an extremely rare disease, many more cases are being reported in recent years.

The etiology is not known. Microscopic examination of excised fibrous plaques presents a picture resembling that of keloids elsewhere in the body. Hence, trauma due to previous infections, passage of sounds or some other factor may well be the cause.

Although present methods of treatment are unsatisfactory, radium therapy given by the technic employed in treating keloids appears to be worth while. More than half the patients treated should receive definite

benefit. Radium treatment of 141 patients over a six year period is described; 44.6 per cent of those traced were not benefited but the remainder were helped. The age of the patient, duration of symptoms before treatment and number of treatments given did not seem to be factors definitely influencing the result.

ROENTGEN TREATMENT FOR EXTENSIVE EPITHELIOMA OF THE LARYNX; RESULTS IN 139 CASES*

ARTHUR U. DESJARDINS, FREDERICK A. FIGI AND LUTHER M. VAUGHAN

CASES AND METHOD OF TREATMENT

The purpose of this paper is to review and analyze a series of 139 cases in which epithelioma of the larynx has been treated with fractional doses of roentgen rays from 1936 through 1945. All the patients had extensive epithelioma—in most cases the neoplasms were so extensive that surgical treatment was not considered advisable. Other patients, who had undergone previous laryngectomy here or elsewhere, were suffering from more or less extensive recurrence; in a large percentage of cases the malignant process had invaded some of the cervical nodes. In many cases obstruction required preliminary tracheotomy.

Tracheotomy.—Among all the patients included in the series of 139 cases tracheotomy was not performed at any time in fifty-six cases; tracheotomy was performed before roentgen treatment in seventy-six cases, during the course of roentgen treatment in only one case, and soon after the course of treatment in six cases.

From the foregoing circumstances it is evident that the cases included in this group could hardly be regarded as favorable; indeed, a more unfavorable group of cases would be difficult to find.

Technic of Treatment.—All these patients were treated with rays generated at 200 peak kilovolts, filtered through a Thoraeus filter consisting of 0.44 mm. of tin, 0.25 mm. of copper and 1.0 mm. of aluminum, at a focal-skin distance of 50 cm. The half-layer value was equivalent to 1.75 mm. of copper. In most cases the treatment was given through two lateral fields (one on each side), each of which measured from 8 by 12 cm. to 12 by 18 cm.; but in a small number of cases the treatment was given through three fields (two on one side and one on the other); when two fields on one side were employed, they were on the side on which the bulk of the malignant process was situated.

During the early part of this period, the roentgen treatment was arranged in different ways in an attempt to find the time distribution, the daily dose, and the total dose which would yield the most favorable results. Most of the patients were treated twice a day for periods varying between fifteen and thirty days, but a certain number were treated once a day for a similar period. Except on Sunday, all patients were treated as much as possible on

* Abridgment of paper published in full in the *American Journal of Roentgenology*, 60: 29-34 (July) 1948.

consecutive days; but sometimes, because of radiation sickness or for some other reason, the course of treatment was interrupted, at or near the middle, for one, two, or three days. Six patients were treated for sixteen days, one for seventeen days, one for eighteen days, thirty for twenty days, one for twenty-one days, two for twenty-two days, twelve for twenty-three days, five for twenty-four days, sixty-five for twenty-five days, two for twenty-six days, one for twenty-seven days, and seven for thirty days.

In six cases treatment was discontinued after ten days in one case, after thirteen days in three cases, after fifteen days in one case, and after sixteen days in one case. This had to be done because the patients' condition had become too bad to continue treatment (five cases) or because the patient refused to carry on (one case).

The total dose given to each field varied from 2,000 to 4,000 roentgens measured in air; in most cases the total dose was greater than 3,000 roentgens. Therefore, when the treatment was given through two fields, the total dose for both fields varied between 4,000 and 8,000 roentgens; when the treatment was given through three fields, the total dose varied between 6,000 and 10,000 roentgens. In normal persons the width, or lateral thickness, of the neck varies between 10 and 16 cm.; but, since most of the patients who were referred for treatment had lost weight, the lateral thickness of their necks varied between 10 and 14 cm. The thickness of the average patient's neck, therefore, is approximately 12 cm. Half this thickness would be 6 cm. With roentgen rays generated at 200 kilovolts and filtered through a Thoraeus filter composed of 0.44 mm. of tin, 0.25 mm. of copper and 1.0 mm. of aluminum, approximately 70 per cent of the air dose would be delivered 0 cm. beneath the skin. Therefore, if an air dose of 3,800 roentgens is given through each of two fields, the total dose reaching the tumor in the middle of the neck would be approximately 5,320 roentgens.

Gradually it was found that there is such a thing as too large a total dose, which causes severe reaction of the mucous membranes and skin without improving the end result. In time it was learned that a total dose between 3,500 and 4,000 roentgens to each of two fields yielded as good results as could be obtained; in the average case such a total dose to each field caused a reaction of the mucous membrane and of the skin which was not unduly severe (moderate epithelitis and epidermitis). In some cases the reaction was only slight, but in a small percentage of cases even this dose caused a rather severe reaction.

The reason why many patients were treated twice a day was the hypothetical reason of trying to irradiate as many cells as possible during the active phase of mitosis. In all probability it would be impossible to recognize clinically any difference in the biologic effect of irradiating a neoplasm once a day or twice a day, but some hypotheses are so appealing! Another subsidiary reason for irradiating the epitheliomas twice a day was that this might cause less systemic reaction (radiation sickness) than exposure to the same daily dose at one sitting. It is now clear that any difference in this respect is too slight to be perceptible clinically.

Coutard and many other radiologists have given total doses of approximately the same magnitude or even larger doses, and they have spread the treatment over a period varying from fourteen to twenty-five or thirty

benefit. Radium treatment of 111 patients over a six year period is described; 44.6 per cent of those traced were not benefited but the remainder were helped. The age of the patient, duration of symptoms before treatment and number of treatments given did not seem to be factors definitely influencing the result.

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The reason why many patients were treated twice a day was the hypothetical reason of trying to irradiate as many cells as possible during the active phase of mitosis. In all probability it would be impossible to recognize clinically any difference in the biologic effect of irradiating a neoplasm once a day or twice a day, but some hypotheses are so appealing! Another subsidiary reason for irradiating the epitheliomas twice a day was that this might cause less systemic reaction (radiation sickness) than exposure to the same daily dose at one sitting. It is now clear that any difference in this respect is too slight to be perceptible clinically.

Coutard and many other radiologists have given total doses of approximately the same magnitude or even larger doses, and they have spread the treatment over a period varying from fourteen to twenty-five or thirty

days, and in some cases as long as sixty days. Most patients can tolerate from 200 to 400 roentgens a day without undue disturbance, many can take 300 or 400 roentgens daily without any sign of intolerance, but in some cases even 200 roentgens a day causes the patient to lose appetite or to vomit. In our experience a daily dose between 300 and 325 roentgens is tolerated by most patients, but sometimes the daily dose must be reduced to 250 roentgens or even to 200 roentgens. In some cases, for this reason, the period of treatment has extended over twenty-five days. It is possible that to have shortened the period of treatment to twenty days, or even less, might have improved the results; but this would have required the patients to take a daily dose of nearly 400 roentgens, and almost certainly many patients would have found it difficult or impossible to tolerate this larger daily dose. Even with a daily dose of about 300 roentgens, many patients have lost weight, and sometimes this loss has been considerable.

During recent years some radiologists have advocated treatment through small fields; or, after starting treatment through fields of a certain size, some have recommended reducing the size of the fields as the neoplasms regress. No doubt, these methods can be used effectively in selected cases, when the neoplasms are not extensive; but in most of the cases with which we have had to deal too small fields would almost certainly have meant that some parts of the malignant process would not have been included or would not have received an adequate dose. In cases of this kind, therefore, the method of diminishing fields would be dangerous. Our attitude has been that, unless the entire neoplasm is treated, the patient might as well not be treated at all. To us, even at the cost of more extensive and more severe reaction, it has seemed preferable—indeed essential—to irradiate through rather large fields in order to avoid the risk of missing part of the malignant process. Even with large fields, we are certain that, in some cases, outlying extensions or infiltrating portions of the neoplasms, or involved lymph nodes, did not receive adequate exposure or were missed altogether.

Tolerance and Reaction.—During the first half of the course of treatment, most patients can eat about as usual, and their weight does not diminish much, if at all. But a small percentage of the patients do not tolerate the treatment well, nausea causes their appetite to diminish, and they lose some weight. Sometimes it is necessary, on account of a low tolerance, to interrupt the treatment for two or more days in order to allow the patients to recuperate enough to enable them to complete the course of treatment. In some cases in which the patients have some degree of obstruction and dysphagia it is necessary, for this reason, to insert a tube through the nose into the stomach, and the patients are fed artificially. This seldom occurs during the first half of the course of treatment. When, between the twelfth and fourteenth days, the mucous membrane begins to react (epithelitis), most patients have an increasing difficulty in eating enough food to nourish themselves adequately. Usually this is because the gradually increasing reaction of the mucous membranes causes swallowing to become more and more painful; but sometimes, in cases in which, before treatment, some degree of obstruction was present, the mucosal reaction causes the obstruction to become complete, or nearly so. It is especially in cases of this kind, and at this stage, that the insertion of a tube for artificial feeding may

become an urgent measure. Some patients may lose from 5 to 15 pounds (2.3 to 6.8 kg.), or even more.

After the entire course of treatment has been completed, the epithelitis and epidermitis continue for two or three weeks, slowly subsiding during this period. By this time the neoplasm has retrogressed more or less; at the same time the patients have less difficulty in swallowing and, as they can take more food, their weight begins to increase. Usually the weight which has been lost before and during the course of treatment, or at least much of this lost weight, is regained within two or three months after completion of the treatment. When, three months after treatment, most of the patients returned for re-examination, most of them had recovered the weight which had previously been lost, their general condition had greatly improved, and the tumor had disappeared. In some cases, however, residual edema made it difficult or impossible to be certain whether or not the malignant process had completely disappeared; when cervical lymph nodes had been affected more or less extensively, the involved nodes usually had diminished and often they also had disappeared. Sometimes, when lymph nodes in the lower part of the neck had been involved, they did not retrogress as much as nodes high in the neck. In some cases, also, affected nodes in the upper part of the neck underwent only partial regression during the first three months, but complete regression of these nodes occurred later. This, however, was not always true. In most cases, when the involved cervical nodes had not disappeared at the end of three months, complete regression did not occur at any time, and subsequently the malignant process in these nodes again became active.

As has already been shown, the most favorable cases are usually selected for surgical treatment, and only the cases which surgeons consider unsuitable for surgical treatment are referred for roentgen treatment. Some of the patients in this series had undergone operation one or more times, and some had undergone laryngectomy. Others had undergone electrocoagulation, with or without implantation of radon seeds. These were referred for roentgen treatment because further surgical measures were out of the question. Under these most unfavorable circumstances, to expect to cure many patients would be sheer folly; and yet, as will be seen, some patients were cured, and many others derived substantial improvement which continued long enough to be well worth the effort to treat them.

The number of cases included in the series which we are reporting is 139. Among these, 120 of the patients were male and nineteen were female. This overwhelming preponderance of male patients agrees with the experience of all those who have written about epithelioma of the larynx. Among these patients eighty-one were from forty through sixty years of age; of those less than forty years were one patient aged thirty-four years, four patients aged thirty-five years, and one patient aged thirty-eight years. Among those who were older than sixty years, seventeen patients fell in the age group from sixty-one through sixty-five years; fourteen fell in the age group from sixty-six through seventy years; thirteen fell in the age group from seventy-one through seventy-five years; six fell in the age group from seventy-six through eighty years; the age of one patient was eighty-one years, and that of the oldest patient was eighty-two years. Thus, fifty-two patients were aged from sixty-one through eighty-two

years. Of the total number of patients in this series, the proportion of those whose ages were seventy-one years or more was 15 per cent.

Regression of Tumors and of Involved Lymph Nodes.—In a large percentage of the cases a course of treatment such as has been described was accompanied by rapid regression of the neoplastic process; by the time the course of treatment had been completed, the tumor had retrogressed so much that it could no longer be recognized. In other cases the treatment was accompanied by substantial regression, but some of the tumor or secondarily involved lymph nodes could still be seen or felt at the time the course was completed. In many of these cases apparently complete regression required about two months after the end of the course of treatment. By this is meant that, about two months after the course of treatment had been completed, clinical or laryngoscopic evidence of the neoplasm could no longer be found. Three months after treatment, in most cases, some degree of residual edema in the larynx and in the soft tissues of the neck was present in a large percentage of cases. This edema slowly diminished, and usually, but not always, it had disappeared at the end of six or eight months. In a small percentage of cases some edema continued still longer.

As far as the patients' symptoms were concerned, these usually subsided in proportion to the degree of regression of the neoplasm and at approximately the same rate. An interesting point, however, is that, even when the malignant process had disappeared, many patients did not recover the normal quality of their voice. Other symptoms, such as hoarseness, cough, dyspnea, or dysphagia, often disappeared or greatly diminished, but many patients were left with a voice which was not entirely normal. Sometimes this was due to the scarring of previously involved laryngeal structures after regression of the neoplasm; sometimes, no doubt, it was due to incomplete regression of the malignant process, even when this could no longer be seen; sometimes it was due to residual edema.

Of the 139 cases a piece of tissue or a lymph node had been removed for biopsy in 126 cases (90.6 per cent). In the remaining thirteen cases tissue for biopsy had not been removed, but in all of these the clinical features were such that the malignancy of the lesion could hardly be doubted. Of the 126 cases in which the diagnosis had been confirmed by microscopic examination of sections of tissue not one had a neoplasm with a malignancy of grade 1 (Broders' method); from this it is apparent that all patients who had tumors with grade 1 of malignancy were treated surgically. In forty-one cases the neoplasms were of grade 2 malignancy, in fifty-five cases the tumors were of grade 3, and in twenty-eight cases they were of grade 4 malignancy. In one case the pathologist who examined sections of tissue from the tumor reported "adenocarcinoma of cylindroma type," and in another case the pathologist reported "grade 1 neoplasm," without further identification.

RESULTS

Of the 139 patients included in this series recent information was obtained about all but five. Although information about these five patients has not been obtained recently, several of them are known to have been alive and well from one to six years since they were treated. Therefore, we

have not hesitated to tabulate them with the other patients, if only to show how long they are known to have survived.

Sixty-one patients are known to have died within one year; some of these died soon after treatment (a few weeks or months), and in one case the patient died before the course of treatment could be completed. In these cases, obviously, the malignant process had been more than usually extensive, and the general condition of the patients had been bad before the treatment was started. This had been recognized, but treatment had been given nevertheless in the hope of obtaining for the patients substantial, though temporary, improvement. The other five patients were living and apparently well when they were last heard from less than one year after treatment; since these patients were treated so recently, however, too much significance cannot be placed on their appearance of well-being at that time.

In some of these cases not only the malignant condition in the larynx had been extensive, but adjacent structures had been invaded, or lymph nodes in the lower part of the neck had been involved. Under these circumstances, the chance of complete regression was small. When, besides extensive local involvement, the process already has extended to lymph nodes in the upper half of the neck, the prospect of cure is not great. But when, besides the foregoing conditions, lymph nodes just above or behind the clavicle have been invaded, complete regression is practically out of the question. In some cases it is likely that, besides lymph nodes in the lower part of the neck, which are known to be involved, other nodes which cannot be seen or felt are also affected.

In thirty of thirty-six cases the patients are known to have died between one and two years after treatment. When the other six patients were last heard from, all were living and apparently well at that time (recently). One of these patients had had exceptionally extensive involvement and how long he may remain well is uncertain. Another of these six patients was operated on at least twice after the course of roentgen treatment for reactivation of portions of the malignant process. It is plain that the thirty patients who died in this second group of cases, together with the sixty-one patients in the first group, who had died within one year, represent a large percentage of the entire series. There is no doubt that these ninety-one patients had died so soon because the malignant tumors with which they had been afflicted had been most extensive. Undoubtedly the grade of malignancy also had played an important part.

The first impression is one of doubt concerning the advisability of treatment in such unfavorable cases. And yet, the great majority of the patients had obtained substantial improvement. In some cases, within two or three months after the completion of treatment, the neoplastic process had disappeared, and the patients' general condition had greatly improved; often this improvement had continued for many months, to be followed by fresh activity of the malignant condition and by death. In other cases treatment had not caused the primary neoplasms and their secondary extensions to disappear completely, but marked regression and general improvement had occurred, and this had continued for a variable period. When, for from several months to two years, treatment is followed by marked or complete abatement of symptoms and by pronounced improve-

ment in general condition, no one can question its value. After all, complete and permanent cure is not the only criterion of a method of treatment; in truth, this criterion is valid only in carefully selected and favorable cases. To practice medicine means, not only to try to cure patients when this is feasible, but also to relieve suffering in any form when a cure is impossible.

Five patients are known to have survived between two and three years, one has thus far survived between three and four years, and three are living and well between four and five years. Four are living and well between five and six years, one is living and well between six and seven years, three are living and well between seven and eight years, two are living and well between eight and nine years, and two patients are living and well between ten and eleven years.

Of the 139 cases in the entire series, seventy-one patients were treated between 1935 and 1942, inclusive; of these we have not been able to obtain recent information concerning three. This leaves sixty-eight patients in the series who were treated during this period and who are living more than five years since their treatment at the clinic. As percentages of "cured cases" go, this proportion is not as high as might be expected but, considering the initially unfavorable character of all these cases and the extensive malignant neoplasms from which the patients suffered, even this percentage seems worthy of consideration. There is no doubt that, if these patients had not been treated in the manner which has been described, all of them must inevitably have perished in short order. Moreover, this percentage does not give any idea of the pronounced relief of symptoms and improvement in general condition which, in the patients who have died, had occurred after treatment.

ROENTGEN TREATMENT OF BRONCHIAL ASTHMA*

EUGENE T. LEDDY AND CHARLES K. MAYTUM

We realize that statistical studies of the results of the roentgen treatment of asthma are only of questionable value and that they may be misleading because of the multiple etiologic factors. We admit also that almost any kind of treatment, even a minor change in the usual medication or the use of a new proprietary remedy, may relieve asthma in a certain number of cases. In the cases which we shall consider, roentgen therapy was used only after specific or nonspecific therapy had failed to produce relief or after a specific cause for the asthmatic attacks could not be found. Most of our cases belong to the latter group. Some of the patients were known to be sensitive but failed to obtain relief of their asthma by specific treatment. In recent years we have employed some type of treatment other than roentgen therapy in practically all cases of asthma but in a few cases roentgen therapy has been the only type of treatment employed. No

* Abridgment of paper read at the meeting of the Radiological Society of North America, Boston, Massachusetts, November 30 to December 5, 1947.

patient with mild asthma was treated with roentgen rays. About half of the patients had severe or very severe asthma; the remainder had moderately severe asthma. Both together constitute about 6 per cent of the total number of asthmatic patients who have been treated at the Mayo Clinic.

In 1936 we reported the results obtained by irradiation of the mediastinum in twenty-three cases of severe asthma. The patients were treated in the years 1931 to 1934, inclusive. Five of them were improved to a great degree for many months; eight were definitely relieved for shorter periods. In the ten remaining cases, the results were classified as failures. In this group of cases, a technic of treatment through paravertebral fields was favored, and a dose of about 550 r was administered in two days. Roentgen rays generated at 135 kv. and filtered through 6 mm. of aluminum were employed. The conceptions on which this treatment was based were as empiric and as indefinite as was our knowledge of the true nature of asthma, but in general the method seemed to produce better results than other methods which we had been using, such as irradiation of the spleen, irradiation of an anterior mediastinal field or irradiation of a combination of different fields. The technic had the additional advantage of producing fewer gastro-intestinal upsets than did the methods previously employed, and, as we have said, it seemed to produce an appreciable relief from the asthma.

In 1939, we reported another series of 215 cases in which the patients were treated in the years 1935 to 1937 inclusive. One hundred and sixty-one of these cases were available for statistical analysis. Thirty-eight (24 per cent) of the 161 patients obtained more than 75 per cent relief which lasted from one to many months. An additional group of twenty-three patients (14 per cent) obtained as much relief but were not included in the former group because other treatment, given at the same time, may have been a factor in relieving the symptoms. The remaining seventy-four patients (46 per cent) obtained less than 50 per cent relief or relief for a very short period, and the results were considered failures.

The 215 patients were treated through a large anterior and a large posterior field over the mediastinum. This technic, which has been termed the "high-dosage" technic, was thought perhaps to produce better distribution of the radiation within the thorax and, therefore, to produce better results. As in the first series, the roentgen rays usually were generated at 135 kv. and as a rule were filtered through 6 mm. of aluminum. A dose of 500 r, measured in air, was given to each field. Only rarely was the liver or spleen treated alone or in conjunction with treatment of the mediastinum.

In another small group of cases of asthma, one anterior field and two paravertebral fields were treated. Irradiation of the fields was given at an angle of 120 degrees. The results in this series were not satisfactory.

In the second study we stated that we were unable to determine any criterion by which we could judge which patients would be relieved by roentgen treatment and which would not, but our impression was that the more severe or more constant the asthmatic symptoms the better was the chance that roentgen therapy would relieve the symptoms. At that time we had no conclusive data by which we could explain the beneficial effect of roentgen rays in cases of asthma but we offered the theories that roentgen rays might decrease the secretory power of the mucous glands in the trachea, or might liberate antibodies from the leukocytes that then

might stimulate the production of eosinophils, or that the benefit might be due to an analgesic effect of the roentgen rays on the nervous system.

Incidentally, it might be mentioned here that for a short time we held the hypothesis that the effect of roentgen rays was due to the production of "protein shock" and that those patients who were most nauseated after treatment obtained the most relief. We, therefore, irradiated hypogastric fields in some cases and splenic fields in others. The nausea produced by this method and the failure of relief to ensue forced abandonment of this idea after a brief experience.

Shortly after our second paper on the roentgen treatment of severe asthma was prepared, we treated several patients who had exceptionally severe asthma and were in precarious physical condition. Because we thought that the usual technic of treatment entailed an excessive risk, we halved the dose usually employed. In all of the cases in which the patients were treated in this manner, the results were satisfactory. This experience led us to adopt the application of a dose of about 250 r to one large anterior and one large posterior mediastinal field. We have used this method of treatment in more than 1,000 cases. This method of treatment has been termed the "low-dosage" technic.

Up to now, we have been unable to establish any criterion by which we could judge which patients would be relieved by roentgen treatment and which would not, but we have the distinct impression that the more severe and the more constant the asthmatic attacks the better is the chance of obtaining relief with roentgen therapy. The age of the patient and the duration of the present attack of asthma seem to make little difference. About 70 per cent of our patients were middle-aged women who had had asthma for many months (in some cases the patients had had the disease for twenty or more years). We did not find that the age or sex of the patient had any effect on the results of treatment. In general, the longer the duration of the disease the better is the outlook after roentgen treatment. However, it should be understood that this remark is subject to great reservation and exception.

A group of cases in which the results of roentgen therapy were unsatisfactory was compared with a group of cases in which the results were satisfactory in an attempt to ascertain whether such factors as anemia, leukocytosis, eosinophilia, fever, sputum, hay fever, bronchitis, emphysema, bronchiectasis, nasal polyposis, sinusitis and drug allergy might play a role in the results, but the results of this comparison were too indefinite to allow any deductions.

TECHNIC OF LOW-DOSAGE ROENTGEN THERAPY

In the low-dosage technic, which we are using at present, a large field (16 cm. square) is centered on approximately the center of the sternum, and a posterior field is arranged at a corresponding level. By this layout of fields, not only the hilar lymph nodes but also a considerable amount of adjacent pulmonary tissue is irradiated. We are certain that the use of large fields produces better results than does the use of narrow fields through which only the hilar region is irradiated. Each field receives a dose of 250 r. As a rule, the treatment is completed in two consecutive days.

We have, on rare occasions, treated both fields in one day. The single

advantage of doing this is that it saves the patient a day; however, this is not the whole story because, as a rule, the nausea and vomiting, which are very likely to follow, penalize the patient for the day he may have saved. Since we think that the asthmatic symptoms are more likely to be aggravated when treatment is completed in one day than they are when the treatment is completed in two days, we do not advise that treatment be given in one day unless the patient has been fully warned of the likelihood of complications.

RESULTS OF LOW-DOSAGE ROENTGEN THERAPY

With the exception of mild nausea, which occurred in about a tenth of the cases in which low-dosage irradiation was used, disagreeable effects are rarely encountered. We are certain that the incidence of all untoward reactions has been far less than it has been with the other technics we have used.

Some improvement in the asthma is usually noticed within a day or two, although the full effect usually is not obtained for from four to five days after the completion of treatment. In a few cases benefit may be delayed for a week or ten days or more. In these cases, the benefit may be due, perhaps, to factors other than roentgen therapy. In another small group of cases the improvement may slowly increase over a period of a few weeks but, as we have said, this is an exceptional occurrence.

As far as we know, there is no parallelism between the promptness of the onset of the improvement and either the degree of improvement or its duration. In many cases the improvement has begun within a week after the completion of treatment and the patients have remained entirely free from asthmatic attacks for many months. In an equal number of cases, a relapse has occurred in a few weeks. In most instances in which relief has been obtained, subsequent treatment also has produced relief but disappointments are not uncommon. A patient may obtain remarkable relief after the first course of treatment but may not obtain any relief after subsequent treatments. On the other hand, he may not obtain any relief at all after the first course of treatment, he may obtain relief after the second course, he may not be relieved after the third and fourth courses but he may obtain long-lasting relief after the fifth course of treatment. Other patients obtain satisfactory relief after all treatments and may return to the clinic for the express purpose of obtaining only roentgen treatment.

We have no good reason for advocating roentgen therapy as a prophylactic or as a precautionary measure to forestall asthmatic attacks in cases in which relief has occurred. As a rule, we prefer to postpone repetition of treatment as long as the relief lasts. We have had no experience with the frequent application of roentgen rays until relief is obtained although other authors have obtained satisfactory results with this method of treatment.

With the doses of roentgen rays which we have used there is no risk whatever of injuring the skin or the thoracic structures. We can accept no excuse for substituting any injury for a relatively benign condition such as asthma; however, it should be most emphatically stated that if treatments are applied too frequently they can do a great deal of harm. Incidentally, one woman has had twelve treatments in a period of three years

without the slightest evidence of any roentgen injury. Future treatments for her will necessitate the greatest caution.

Our experience in the treatment of asthma with roentgen rays in all essentials has been similar to our experience in the treatment of inflammatory and infectious lesions in which our results have improved as the doses of roentgen rays have been lowered. For this reason, we think that a lower dose, possibly in the neighborhood of 100 r, or even less, may be worth a trial in another series of cases of chronic, severe, intractable asthma.

ROENTGEN THERAPY OF MALIGNANT TUMORS OF THE TESTIS*

EUGENE T. LEDDY

Within a short period after roentgen therapy first was used in cases of tumor of the testis, it became obvious to many observers that true malignant teratomas are much less susceptible to the action of roentgen rays than are seminomas. The fact that seminomas are highly radiosensitive was noted by Chevassu in his thesis. The radioresistance of teratomas, on the other hand, was emphasized by Desjardins, Squire and Morton about twenty years ago.

Seminomas and malignant teratomas together constitute about 95 per cent of all malignant tumors of the testis. Seminomas are encountered about six times more frequently than malignant teratomas. Both of these tumors occur during the years of greatest sexual potency but the maximal incidence of teratomas occurs earlier in life than does the maximal incidence of seminomas.

Broders has divided tumors of the seminal epithelium into three main groups: (1) teratomas, (2) adenocarcinomas of the seminoma type, and (3) adenocarcinoma of the testis. The teratomas were subdivided into two groups: (1) benign teratomas, and (2) malignant teratomas.

The adoption of Broders' classification, it seems to me, would go a long way toward correcting the confusing and contradictory views about testicular tumors.

I regard the report of the microscopic examination of intact testicular tissue as of fundamental importance in planning roentgen therapy for a patient with a tumor of the testis, because there are, on the one hand, the seminoma which is radiosensitive and has a relatively good prognosis, and, on the other hand, the malignant teratoma which is usually resistant and has a poor prognosis. A distinction by the pathologist of seminoma from malignant teratoma, therefore, gives the basic indications on which roentgen therapy may be planned.

Since there is no way by which the extremely important diagnostic, therapeutic and prognostic questions can be settled with finality other than by histologic examination of tissue obtained from the testis, it follows as a

*Abridgment of paper published in full in the *American Journal of Roentgenology*, 60:39-44 (July) 1948.

corollary that the tissue should be intact, should not be altered by extraneous influences and should be truly representative of the structure of the tumor in question. It is the opinion of physicians who have treated patients with these types of tumors that suitable tissue is best obtained by simple orchiectomy without preoperative radiation.

Simple orchiectomy, in addition to providing information that is of value from a diagnostic and prognostic standpoint, eliminates infection and discomfort in cases of a large scrotal tumor. In addition, it removes a focus from which metastasis may take place. Because a diagnosis of the presence or type of testicular tumor cannot always be made after the histologic appearance of the tumor has been changed by irradiation (a fact that was emphasized by Nash), orchiectomy is advised both as a diagnostic and therapeutic procedure even in the presence of known metastatic lesions in all but very exceptional cases. As far as can be determined from the literature, most American surgeons prefer simple orchiectomy to a more radical operation.

At the Mayo Clinic, shortly after operation (usually a few days) we administer a course of radiotherapy. Recently malignant teratomas have been exempted. For this course of treatment, radium was used in the early days, but because roentgen therapy is, as a rule, more practical, more efficient, and more expedient than radium therapy, radium is now seldom used except for the occasional treatment of a small metastatic lesion in the supraclavicular region or, possibly, for a small localized recurrent lesion in the scrotum. This procedure is in accordance with the general practice of most radiologists.

For a long time it has been the view of the members of the Section on Therapeutic Radiology of the Mayo Clinic that the technics of palliative and curative treatment should often be different; that a radiosensitive and a radioresistant tumor should not necessarily be treated in the same way; that an old or debilitated patient should receive milder treatment than a young or vigorous one; that clinical, physiologic and pathologic data are of equal or even of greater importance than are most physical factors in outlining the treatment for a patient; that the patient should not be killed by a lethal dose of roentgen rays in order to obliterate the tumor; that the quantitative aspects of dosage often are less important than the method by which treatment is given; that injury of the skin is generally of less importance than severe injury of the formed elements of the blood or permanent injury of a viscus adjacent to the tumor; that injuries to the patient are in general directly proportional to the magnitude of the radiation that is absorbed; that in comparable doses high voltage roentgen rays are more injurious to deep-lying structures than are moderate voltage roentgen rays; that a technic suitable for carcinoma of the pharynx cannot be applied without much modification and reservation to the treatment of sensitive tumors in the abdomen, because of the different geometric and physiologic considerations involved; that the application of gamma rays (or roentgen rays approaching the wavelength of gamma rays) as such confers no immunity on either the skin or on normal structures and does not increase the radiosensitivity of any tumor; that the best clinical indication of the magnitude of the volume or the tissue dose is the leukocyte count, and, finally, that precise radiotherapy is subject to all the variations,

confusions and disappointments of other methods of treatment used in all other clinical fields, because the living world knows no constants. For a long time we have regarded these truths as self evident; they are the basis of our ideas about radiotherapy but it must be admitted that they are at variance with those of many radiologists.

It is my present opinion that irradiation of seminomas of the testis and their secondary deposits is best carried out as a rule with roentgen rays of moderate voltage (130 to 140 kv.). This opinion is based on a rather large experience. This type of treatment is used because I know of no proof of the superiority of higher voltage roentgen rays, particularly rays generated at 200 kv. or more. Sometimes, in fact, I have seen patients with metastatic lesions in the abdomen who have not responded well to large doses of high voltage roentgen rays that have been administered elsewhere and I have observed that the application of moderate doses of rays generated at 130 kv. caused the lesions to disappear. Furthermore, prophylactic postoperative treatment, if it is to be truly protective against metastasis, should be applied to *all* lymphatic pathways through which metastasis may take place. This, obviously, makes extensive treatment necessary. The risk of such treatment is greater with rays generated at higher voltages, because the irradiation of the fields which usually should be irradiated as a prophylactic measure produces more reaction and more destruction of leukocytes and increases the risk of injuring normal viscera. I do not feel that a patient should be subjected to the risk of injury from roentgen treatment unless there is some valid indication for such an injury, and to my mind prophylaxis should not necessitate injury.

At the clinic we routinely irradiate four anterior abdominal fields extending from the xiphoid cartilage to the pubic region (two each side of the midline*) and four corresponding posterior fields. The mediastinum and the left supraclavicular space also are always treated. Each field receives a total dose of about 540 r (in air). One or two fields are treated daily, depending, of course, on the patient's tolerance and especially on the leukocyte count. This course of treatment is repeated in a month. If metastatic lesions have been present in the abdomen before operation, a third course is given after a lapse of two months.

For seminomas of the testis, the doses used at the clinic are low in comparison with those used elsewhere; we feel that the use of rays generated at high voltage or more intense treatment generally is not indicated for seminomas—the high radiosensitivity of which has been universally recognized—since not only are the published results of more intense treatment used elsewhere no better than our results but the technic usually entails more risk to the patient. Incidentally, in the treatment of at least 500 testicular tumors in a period of twenty years, we have never had a death which could be attributed in any way to roentgen therapy. That our methods of treatment have proved satisfactory is confirmed by the statistical study which Cabot and Berkson made of the results of treatment of these lesions. They found that in all cases of seminoma of the testis the five-year survival rate was 67.7 per cent, whereas in cases of all other malignant tumors of the testis the five-year survival rate was 29.3 per

*These are omitted if we are quite certain that there are no metastatic lesions in the abdomen.

cent. Of all patients who had seminomas and who received roentgen therapy, 71 per cent lived five years or more. In the cases in which roentgen therapy was not employed, the five-year survival rate was 58.8 per cent. In general, in cases in which there is no evidence of abdominal metastasis at the time of irradiation, the three-year survival rate is twice as high as it is in cases in which metastatic lesions are present in the abdomen. Two thirds of the patients who do not have metastatic lesions in the abdomen live at least three years. The presence or absence of metastatic lesions in the abdomen obviously is of the greatest importance both from the viewpoint of roentgenologic technic and of prognosis.

The symptoms of metastatic involvement of the para-aortic lymph nodes have been ably described by Desjardins and their importance has been pointed out by Nash and by Scheetz.

Involvement of these nodes by metastatic deposits from testicular tumors probably takes place earlier in cases of malignant teratoma than it does in cases of seminoma. Involvement of these nodes frequently produces a dull aching pain in the back which is often called "lumbago" by the patient. The pain may extend into the hip or leg and is often attributed to sciatica. Bloating, belching, fullness in the abdomen after meals, and constipation commonly occur after the para-aortic nodes have become involved. When the epigastric nodes are the site of secondary deposits, symptoms referable to the abdominal viscera may occur so suddenly as to simulate an acute disease of the abdomen. Desjardins has pointed out that, although it is sometimes difficult to be certain of metastatic involvement of the para-aortic lymph nodes in many cases, a diagnosis can be made on the basis of the history and the physical findings. When a definite mass cannot be palpated, only deep abdominal resistance may be found and pressure by the examiner's hand at the site of this vague resistance elicits tenderness which is not found when similar pressure is made on a normal abdomen. When the metastatic lesion in the abdomen has become sufficiently large it may be palpated easily as a smooth or irregular firm, immobile mass, lying most often on the side of the abdomen corresponding to the diseased testis or toward the midline in the epigastric region. In certain cases, special technics of roentgeography or urography may give definite indications of metastatic involvement of the para-aortic lymph nodes.

In the presence of any of these signs or symptoms, the best practice is to institute treatment for a metastatic lesion; even if the evidence regarding the presence of such a lesion is vague or inconclusive, it is advisable to institute treatment.

Metastatic involvement of one or more of the left supraclavicular lymph nodes is the forerunner of involvement of the peribronchial nodes and is usually secondary to involvement of the lymph nodes in the upper part of the abdomen. The enlargement of left supraclavicular nodes of a man is an urgent indication for examination of the testes. In cases of malignant teratoma, involvement of the supraclavicular nodes occurs more often and earlier in the course of the disease than it does in cases of seminoma.

Enlargement of the inguinal lymph nodes is not definite evidence of involvement by metastatic deposits from testicular tumors. Such metastasis is evidence that the tumor of the testis has perforated its capsule and has

spread to trunks draining into the groins. The diagnosis of metastatic involvement of the inguinal nodes, therefore, should be supported by definite evidence that the tumor actually has involved the capsule and also by biopsy of an enlarged lymph node.

Since it is well known that seminoma of the testis responds well to roentgen therapy, the therapeutic test can often be used with high accuracy to judge the nature of metastatic lesions when their histopathologic structure is unknown. Some tumors may be a mixture of a seminoma and a teratoma. In this case, the initial response of the tumor may be satisfactory because the seminoma is destroyed; however, after the initial response has taken place, the residual tumor, which is made up of more resistant cells, may not respond and the tumor may grow in spite of treatment.

For the treatment of seminomas, roentgen therapy has assumed a position of prime importance and has altered the prognosis from one of hopelessness to one of subdued optimism.

This is quite different from the prognosis of malignant teratoma of the testis. The study by Scheetz showed that the experience of roentgenologists in the past few years and the results that they have reported confirm the remarks which Desjardins, Squire and Morton made twenty years ago about the lack of response of these tumors.

It might be stated in brief that no technic of treatment which we have used within the limits of safety has been more than temporarily effective in the treatment of metastatic lesions caused by malignant teratomas.

Scheetz, who reviewed fifty-four cases of proved malignant teratoma, concluded that the only manner in which a cure may be obtained in cases of malignant teratoma of the testis is by performing orchiectomy before metastasis has occurred. He said that this objective can be attained in less than a third of all cases. He did not think that roentgen therapy appeared to have any beneficial effect on malignant teratoma of the testis, which is extremely resistant to roentgen rays. After metastasis, death usually occurred within eighteen months. Ironically enough, in the case in which the patient survived for the longest time, that is for twenty-four years, postoperatively, radiotherapy was not employed. Scheetz felt that the patients who lived for an appreciable period after operation were fortunate enough to have undergone orchiectomy when the teratoma still was confined to the testis. In the cases in which the patients had died, it seemed likely that metastasis had occurred before operation was performed but that the metastatic lesions had not been large enough to produce clinical signs or symptoms at the time when the patients first were examined at the clinic.

Since the radiosensitivity and, therefore, the prognosis of seminomas are completely different from the radiosensitivity and prognosis of malignant teratomas, we feel that our insistence on accurate pathologic diagnosis as a basis for roentgen treatment is justified. Because the method of treatment we use is as effective as any reported, is safer than many types of treatment and is based on extensive experience, we can see no sensible reason for changing it.

CLINICAL APPLICATION OF ATOMIC ENERGY*

FRANK H. KRUSEN AND GORDON M. MARTIN

EMPLOYMENT OF ATOMIC ENERGY IN BASIC AND CLINICAL RESEARCH

The form of atomic energy that is of most interest to those in the medical and biologic sciences are the radioactive isotopes. Greatest emphasis probably should be placed on the promise afforded by the use of isotopes as tracers in the fields of pure chemistry and biologic and medical chemistry. The value of these new tools for acquiring information has so broadened the fields of chemistry and physiology that almost limitless advances can be anticipated. Certainly the ability to investigate the dynamic equilibrium of chemical and biologic processes has brought us to a new frontier.

Since radioactive isotopes emit rays that can be detected, they can be followed in the organism. The result is that a new approach to the study of metabolic processes has become available. Lawrence has pointed out that only one in several million atoms needs to be labeled with activity to enable all of the atoms to be followed. In tracer work, extremely weak activities of the elements are used so that there are no biologic effects from the irradiation. Lawrence has described several methods or technics which have been devised for providing practical methods of studying the radioactive isotopes being used in research problems. First is the autoradiographic technic in which a dose of the tracer is given and later the tissues are sectioned and placed against a photographic plate for a short period. When the film is developed, one can demonstrate visually the location of the radioactive material in the tissues. This can then be compared directly with a stained microscopic section from the same tissue. Axelrod and Hamilton have reported on studies done with lewisite gas and mustard gas which were labeled with tracers. These were painted on the skin and, later, biopsies were performed. Autoradiographs revealed that the mustard gas was primarily in the corium while the lewisite appeared in the follicles.

The most widely used technic is the *in vitro* method in which samples of material such as blood, spinal fluid, urine or tissues taken at various times after administration of radioactive material are weighed, ashed and measured for radioactivity.

The third method is the *in vivo* method in which the Geiger counter measures the uptake of the radioactive tracers at local areas of the body. This method has been used to measure the time required for the venous blood in a normal person to flow from the arm to the heart after injection of a small amount of radioactive sodium chloride in isotonic saline solution. Circulation to the extremities may be studied by intravenous injection of this solution or by inhaling one of the radioactive gases. Lawrence has reported on the use of this method in correlation with cutaneous temperature readings as a clinical method for studying the adequacy of circulation in peripheral vascular disease and in evaluating the therapeutic measures employed.

* Abridgment of paper read at the joint meeting of the New York Society of Physical Medicine and the Seminar on the Progress of Physical Medicine of the New York Poly clinic Medical School and Hospital, New York, New York, December 3, 1947.

Kiehn, Friedell and MacIntyre of Western Reserve School of Medicine have recently reported some studies on the viability of bone grafts as demonstrated by the location of the deposits of radioactive phosphorus. They noted in one case that twenty-four hours after transplant, the bone graft had taken up an amount of radiophosphorus equivalent to about 60 per cent of that taken up by the same weight of normal iliac bone. It was also found that the uptake of radiophosphorus by killed or devitalized bone grafts was only 7 per cent of the uptake by normal bone. Refrigeration of bone grafts depresses the viability of the grafts for about a week but after that the transplanted bone recovers its vitality and becomes part of the body.

Bollman has employed radiophosphorus in the study of the metabolism of resting and exercising muscles, permeability of muscle during shock and many problems of phospholipid metabolism.

At the Mayo Foundation, Higgins, Larson and Keating have conducted studies dealing with various phases of the employment of radio-iodine in the diagnosis and treatment of thyroid disease. These studies have thrown considerable light on the manner and rate by which inorganic iodine is converted into diiodotyrosine and thyroxine. The method has been and is receiving extensive use in investigation of the relationship between the thyroid gland and the anterior hypophysis. It has been the definitive tool for showing the mode of action of thiouracil and other thyroid inhibitors.

The rate at which radio-iodine enters and leaves the thyroid gland can be followed continuously. Such studies were impossible before manufacture of radio-iodine. Once proper information was available, a method of utilizing larger amounts of radio-iodine in the treatment of hyperthyroidism was developed.

It has been stressed by Allison and by Cohn that there are tremendous possibilities of utilization of radiocarbon because, among the many atomic species which make up living matter, carbon occupies a unique position owing to the enormous number of compounds it can form. Cohn expressed the opinion that it is possible that discoveries made in researches with the carbon isotope C^{14} may be as important and far-reaching as the discovery of fission itself. However, because of its long life, use of C^{14} therapeutically may be extremely dangerous.

THERAPEUTIC APPLICATION

Rhoads and Solomon stated that to date only two artificial radioisotopes have been proved without question to be of therapeutic value. These are P^{32} with a half-life of 14.3 days, and P^{33} and P^{31} , with half-lives of 12.6 hours and 8.0 days, respectively. Until recently, only limited quantities of these two isotopes have been available from the costly and time-consuming cyclotron bombardment. Now, existing piles can provide amounts of these isotopes which will be adequate for medical needs.

Of the disorders which can be treated effectively with P^{32} , polycythemia vera alone has been controlled for long periods. In leukemia, some evidence has been found that treatment with P^{32} results in fewer undesirable side effects than occur when roentgen rays are employed in treatment but there is no greater prolongation of life. Radio-iodine is notably useful at present only in the treatment of hyperthyroidism. Cancer of the thyroid gland,

on the other hand, has not been cured by treatment with radio-iodine, though a noticeable palliative effect has been apparent in a few cases. Keating has recently stated that the results to date in the treatment of cancer of the thyroid have been very disappointing.

Hall and his associates at the Mayo Clinic have employed radiophosphorus as a therapeutic agent since 1941. The most favorable results have been observed in treatment of polycythemia vera. Of 103 patients treated to date, 80 per cent obtained satisfactory remissions lasting for periods ranging from five months to four years. Partial remissions were obtained in the remaining 20 per cent. With recurrence of the polycythemia vera months or years later, remissions were induced a second time after further treatment with the isotope. In treatment of chronic forms of leukemia, remissions similar to those observed after roentgen therapy were induced with radiophosphorus.

Radio-iodine appears to have a definite place in treatment of exophthalmic goiter, at least in certain selected cases. These selected cases probably will include those in which the risk of thyroidectomy is excessive, either by reason of the seriousness of the hyperthyroidism or because of the existence of serious complicating conditions such as heart disease. It may prove to be the treatment of choice for patients whose hyperthyroidism has recurred after thyroidectomy. In this latter group, results obtained with thiouracil have been particularly disappointing.

THE MEDICAL GROUPS WHICH WILL EMPLOY ATOMIC ENERGY

Several different specialty groups in medicine are concerned with atomic energy and radioactive materials. These include the therapeutic radiologist, the radiation physicist, the internist, the physiologist and the industrial physician. Until more is known concerning the immediate and remote effects of radioisotopes, it will be well for all institutions which are employing atomic energy, either for treatment or for experimentation, to have a team of workers including, at least, a radiologist, an internist and a physiologist to provide the necessary safety precautions and to control all methods of using atomic energy.

Radiologists will be concerned primarily with dosage, safety and general supervision of administration. Radiation physicists will assist in problems of dosage and in methods of protection of patients and workers. The internists, especially those interested in hematology and in diseases of the thyroid gland, will be interested in therapeutic applications of radioisotopes. Physiologists will wish to employ radioisotopes as tracers in numerous types of laboratory experiments, and, finally, all industrial physicians will wish to become familiar with the hazards of employment of atomic power in industry and the dangers to workers who are manufacturing radioactive materials.

THE DELETERIOUS EFFECTS OF ATOMIC ENERGY

Finally, from the general medical standpoint, all physicians will be interested in the possible deleterious effects of atomic energy on human beings. Nuclear physicists are working with rays or ionizing particles and their exact capacity for damage is quite unknown. Such irradiations influence cytochemistry, chromosome development and gene mutation. In

examinations of the blood, at least as much significance should be attached to the appearance of any bizarre or unusual leukocytes as to the more commonly reported changes in their total number. All experimental evidence to date suggests that the damaging effects of radiation are exerted on the young, dividing cells rather than on the mature cells which are circulating. Damage at an early stage, if it does not kill the cell, may render it incapable of complete maturation. Generally it is considered that the lymphocyte is the most radiosensitive cell because reduction of number of lymphocytes is the earliest, the most marked and the most consistent change in the blood induced by therapeutic doses of radiation, but lymphocytes are able to recover rapidly.

CONSTRUCTIVE VERSUS DESTRUCTIVE USES OF ATOMIC ENERGY

Not only the power of atomic energy to benefit mankind, but also its power to destroy it, should be recognized. That which has been most fascinating concerning atomic energy is its tremendous potency. An escapist who wishes to doubt the destructive power of atomic energy and thinks that the reports on the Hiroshima bombing were "mostly propaganda" should know these facts. Of the 150 physicians in Hiroshima at the time the atomic bomb fell, sixty-five were killed and most of the rest were injured so severely that they could not treat other injured people. Of 1,780 nurses, 1,634 were killed or hurt too badly to carry on.

Physicians may well stand in the forefront of the ranks which will align themselves in the battle to turn this mighty force from man's destruction to man's benefit.

PRELIMINARY STUDIES ON THE HEATING AND CIRCULATORY EFFECTS OF MICROWAVES—"RADAR"*

URSULA M. LEDEN, J. F. HERRICK, KHALIL G. WAKIM AND FRANK H. KRUSEN

This latest development in heating of living tissues by microwaves has followed in logical sequence. During a long period of study of the application of higher and higher electrical frequencies in medicine, we have finally reached this very short wavelength.

At last we have a means of heating tissues in which we can obtain accurate localization by direction of a beam of energy toward any surface of the body. The fact that it is possible to focus such radiation may permit even more accurate localization and certainly in the future we shall want to investigate the possibility of cross-firing two beams at a given spot. The fact that the radiation can be carried for considerable distances along a wave-guide and deflected through a coaxial cable with a director at the end might permit employment of a large microwave machine for treatment of several patients.

The fact that at this particular frequency "the absorption of radioenergy

* Abstract of paper published in full in the *British Journal of Physical Medicine and Industrial Hygiene*, n.s. 10:177-181 (Nov.-Dec.) 1947.

in water at 100° F. is in the order of 7,000 times the absorption at 27 megacycles now commonly used for short wave diathermy" is of great significance. If we can get better absorption, it is to be expected that we shall have more efficient heating.

We believe that microwaves are suitable for heating of living tissues and we have already inaugurated clinical studies of their application. The wide variety of patterns for heating of tissues and the possibility of placing the microwave director in any position will provide wide flexibility in therapeutic application. A patient will be completely free to move away from the director at any time. Freedom from pads, encumbering cables and toweling commonly used with short wave diathermy will permit more rapid cooling of the skin. The radiation from the single microwave director can be heamed and localized in the manner of a spotlight, thus facilitating clinical application.

Our studies indicate a desirable relationship between cutaneous and internal temperatures which permits adequate internal heating without undue heating of the cutaneous surface. It would seem that heating by microwaves offers promise of considerable usefulness in the practice of physical medicine.

THE PRESENT CONCEPT OF TREATMENT OF POLIOMYELITIS*

EARL C ELKINS AND KHALIL G. WAKIM

In discussing the treatment of poliomyelitis it should be clearly understood that as yet no satisfactory treatment of the disease per se has been found. The major portion of the after-treatment of poliomyelitis is that done to salvage what remains of the function of the weak and paralyzed muscles and to train or reconstruct the involved parts to the point where the patient obtains the best possible function from what he has left. Undoubtedly none of the treatments used, for example, supportive, physical or orthopedic, have any effect on the progress of the disease once it has started nor can treatment change the already existing primary lesions in the central nervous system.

There are no drugs that have any specific effects on the disease and the use of immune serums has not yet met with any great success. Therefore, when the present trends of the treatment are discussed, the trends in the physiatrie and orthopedic treatment must be presented primarily.

During the past six or seven years there has been much controversy relative to the methods of administering the physical treatment. This has been stimulating and helpful in many respects. The changes in the treatment have appeared radical to some workers. This has been due mainly to claims that have been made and to the publicity put forth. Actually the treatment used by outstanding workers ten to thirty years ago did not basically

* Abridgment of paper published in full in the *Journal of the Iowa State Medical Society*, 37: 356-362 (Aug.) 1947.

differ a great deal from that which is used today. The main difference was the tendency to use longer periods of immobilization, to be less meticulous in the re-education of the involved part and to pay less attention to so-called muscular spasm or tightness and to the resulting muscular imbalance produced by this condition.

Practically the whole Kenny concept of the disease, as it was originally described, has been questioned and refuted. However, some of the terms used in the description of the Kenny concept have come into common use; for example, the term "in-co-ordination" instead of "substitution." Undoubtedly both conditions exist—substitutionary movements being a compensatory factor, although, if used too early, they may promote atrophy of disuse of the muscle for which the movement is substituted. The term "muscle spasm" is now used frequently and has caused considerable confusion. The term "mental alienation" is not used as widely because it has not been explained adequately from the physiologic standpoint.

Whether one agrees with the Kenny concept of the disease or not, credit should be given to it for having stimulated a great deal of investigation on the function of neuromuscular mechanisms involved and on attempts to explain the symptoms of the disease further. Some of the basic experimental and clinical studies which have been made are responsible for the changes in the treatment.

TREATMENT

For the past thirty years the main feature in the treatment of poliomyelitis has been considered to be the re-education and training of weak and paralyzed muscles. The clinical results tend to indicate that prolonged immobilization was not rational. Likewise stretching the muscles in the early stages of the disease apparently is not as dangerous as was believed although strenuous stretching of contracted muscles of old poliomyelitic patients may be dangerous. The use of hydrotherapy in the form of therapeutic pools still remains an important adjunct in the treatment of poliomyelitis when properly supervised.

Certainly it is obvious that in the treatment of acute poliomyelitis the supportive treatment used in any infectious disease is necessary. Careful observation of the patient for respiratory difficulties is most important. It was recently pointed out that all the deaths occurring in a series of 461 children less than sixteen years of age in the epidemic of 1946 were due to bulbar paralysis and that it seemed remarkable that attention heretofore has been primarily focused on morbidity rate rather than mortality rate in poliomyelitis.

It was emphasized that in the care of bulbar poliomyelitis, the crucial problem is the prevention of anoxia, the susceptibility of brain tissue to anoxia being common knowledge. Therefore, severe bulbar poliomyelitis implies encephalitis involving the brain stem and it would seem logical to maintain a continuous supply of oxygen. The treatment administered was based on the correction or prevention of anoxia due to one of several factors: (1) an impaired central respiratory mechanism with resultant inadequate oxygenation due to periodic or complete apnea; (2) an impaired peripheral respiratory mechanism (paralysis of respiratory musculature); (3) the repeated aspiration of small amounts of mucus with production of numerous

small regions of obstructive atelectasis, plugging of large bronchi by mucus or food particles, accumulation of mucus in the oropharynx with consequent mechanical obstruction, paralysis of the vocal cords with obstruction of airways or reflex closure of the glottis; (4) pulmonary edema with consequent decrease of alveolar absorptive surface. Combating these factors was the basis for these workers using aspiration, administering oxygen, performing tracheotomy and using the respirator.

Tracheotomy was performed twenty times in the series of 107 cases in which there were bulbar symptoms. The indications for tracheotomy were based on the signs and symptoms indicating the presence of imminent possibility of anoxia; for example, irregular shallow or periodically apneic respiration or both; exhaustion, agitation, restlessness, or apprehension, progression of bulbar involvement with increasing dysphagia, and the presence of suffusion and cyanosis. In general all patients who had bulbar poliomyelitis were given oxygen prophylactically. It was concluded that there can be little doubt as to the effectiveness of tracheotomy in certain cases of bulbar paralysis; that is, in those not characterized clinically by fulminating progression. It was implied, of course, that no treatment is effective in cases of fulminating bulbar poliomyelitis.

The patient should be carefully watched and the respirator should be used before the symptoms of a serious lack of oxygen become obvious. It would appear that too frequently the respirator is not used sufficiently early, because it is considered a major procedure and is used only as a last resort.

The general medical care of a large percentage of patients who have acute poliomyelitis consists of general supportive treatment with use of sedatives and analgesics for pain if necessary. The more specific procedures consist of physical supportive measures to maintain good bodily alignment and to prevent the formation of deformities and the use of moist heat, mainly hot packs and mild passive exercise.

Measures should be taken in cases in which paralysis is present to provide proper support of the extremities and to maintain correct bodily alignment. The use of a board under the mattress to maintain correct bodily alignment, a footboard to prevent drop foot and to prevent bed clothes from pushing the foot down, rolled towels, sand bags, pillow supports and at times the use of wire and plaster splints to keep the extremities in proper position, are important. The position of the patient may be changed at frequent intervals during the twenty-four hours of the day. However, care should be taken that malposition is not maintained or frequently repeated for any length of time. The greatest difficulty encountered relative to improper alignment occurs in young children, who are more active than older patients and do not understand what is being done. They may lie in poor position or stand on the soft mattress on weak and paralyzed extremities; repetition of such positions may produce deformities. It is obvious that good nursing care, close observation, careful restriction of movement and use of some form of splinting by means of the simple supports mentioned previously are essential. Rigid supports may be used but it must be emphasized that "rigid supports are a poor compromise for good care."

There seems to be a general consensus that the use of hot packs does relieve the pain and discomfort of acute poliomyelitis.

The method of applying the packs has changed. The meticulous procedure of applying hot packs to the various segments of the body is not as widely used as previously. In the past several years the so-called prone packs have been used. In this procedure the woolen cloths rung out of boiling water are merely dropped on the area and an insulating material is wrapped or tucked around them. In treating small children the older type of pack carefully wrapped on the part still is necessary. During the acute phase of the disease most workers apply the packs for periods of six to twelve hours daily and change them every fifteen minutes to two hours depending on the severity of the pain and tightness. The frequency with which the packs are changed and the time they are applied each day should depend somewhat on the condition of the patient. If the pain, tenderness and muscle tightness are not severe it may not be necessary to treat as vigorously. Obviously if the patient is in serious condition resulting from respiratory involvement hot packs should be used with caution. Likewise, in the case of the patient in the respirator, packs should be used with caution; however, they may be used to advantage in certain instances to prevent stiffness although the procedure is difficult under such conditions.

The total length of time during which the packs may be used seems to vary. A few years ago it was considered essential to use packs for weeks and months in order to obtain relaxation of tightness. There has been a trend away from this concept and toward the belief that other factors are as important as, if not more important than, hot packs in release and prevention of residual muscular "spasm."

Whereas hot packs are still applied over long periods, where available it has been found that warm baths used in conjunction with mild passive stretching exercise are as effective as hot packs if not more so. This is especially true after the acute stage of the disease has passed. However, in the majority of cases of poliomyelitis, if proper treatment is given—for example, using hot packs or warm baths or both, and carefully done passive exercise—the pain, tenderness, and muscular tightness usually disappear in two to eight weeks. It should be emphasized that in many instances heat alone will not eradicate muscular tightness.

It has been fairly well established that passive stretching exercise, preferably done following whatever thermotherapy is given, is very important. Whereas stretching of tight muscles was not considered part of the treatment in the early stages of the disease a few years ago, it is now used in varying degrees by nearly all workers. Passive stretching exercise must be done carefully but it can be used from the early stage of the disease. As the pain subsides it can be continued until the muscle tends to remain supple and full length. After the painful stage of the disease has passed, careful stretching of the muscles apparently can be done rather strenuously without danger of injury.

Since so much emphasis has been placed on muscular tightness and spasm, several drugs have been used in an attempt to produce rapid relaxation. The two most widely studied drugs were prostigmine and curare. The use of prostigmine and hot packs is still being studied. Such treatment has not yet proved to be very effective.

Crystalline d-tubocurarine chloride has been used recently with considerable enthusiasm. When administered intramuscularly in oil in small

doses and in conjunction with passive stretching exercise curare was considered to be spectacular in its effect in relief of spasm and other symptoms of the disease. However, in a small series of cases the use of curare alone, intramuscularly, intravenously or intravenously in combination with pentothal sodium anesthesia and with passive stretching exercises, did not appear to be of any more value than the use of hot packs or some other form of heat and stretching exercises. Fox used it in a series of cases and concluded that it may be of temporary benefit in some instances but that its use in the acute phase of the disease cannot be recommended. It must be remembered that curare is a potent and dangerous drug and must be used with caution.

Treatment after the acute stage, in addition to attempting to relieve pain and muscular tightness, should have as its aim the establishment of co-ordinated muscular function. This is undoubtedly one of the most important phases of the treatment. It is in this phase of the treatment and in that of relief of muscular tightness that the greatest strides have been made, not because of any great discoveries in bodily mechanics or functional anatomy but because of the great stress laid on the necessity for co-ordinated muscular action and its role in efficient muscular activity. The results obtained from this stage of the treatment are largely dependent on the success and thoroughness with which pain and soreness have been relieved and full mobility of the involved parts has been gained. Patients can learn to do well when they are well co-ordinated even though they may have little actual muscular power.

There is evidence to indicate that in poliomyelitis and other conditions in which there is partial or complete disruption of the peripheral nerves, the in-co-ordination is due to disordered reciprocal innervation.

Time does not allow a discussion of the procedures used to train patients in co-ordinated movement. It is done largely by stimulation of the proprioceptors in various muscles through careful passive motions. This is done frequently and the muscles are pointed out to the patient. These passive motions and carefully guided and active motions assist in establishing the co-ordinated patterns of movement. The patient's activities are carefully guarded in order that he may not develop undesirable patterns of movement which may readily occur if he is allowed to assume activities too strenuous for the stage of recovery.

Training of patients in co-ordinated movement, in such a manner that all groups of muscles function to the best advantage and the weakened muscles are used and developed properly, requires specialized skill on the part of the physical therapist and careful observation and judgment on the part of the attending physician. It may require weeks and months and it may be difficult to decide whether maximal benefits have been reached.

Another phase of the treatment is that of attempting to increase the strength of muscles. This has always constituted an important phase of the aftertreatment of poliomyelitis. The methods used in strengthening the weakened muscles do not differ greatly from those which have been used for many years. However, more emphasis has been placed on this training and more care is taken in doing it; also it is done for a longer period. This is accomplished first by using careful passive tugging of the weakened and paralyzed muscles to establish the proprioceptive sense. Then active exer-

cise of the individual muscle or groups of muscles is used as voluntary control returns. The amount of exercise depends on the power of the muscle. It is increased as muscular power is increased; that is, from movements with assistance to those with gravity eliminated and then to movements against gravity and resistance. Careful attention must be given at all times to see that the motion is co-ordinated. As muscular power increases in-co-ordinated motions may develop. Since muscles do not recover at the same rate, it can be readily seen that the so-called in-co-ordinated motions can be developed at any stage in the over-all recovery of the various groups of muscles.

As muscular strength returns and co-ordinated movement is established, the activities and functional capacities of the patient are increased. The stage when general activity of the patient is increased seems to vary considerably with the different medical centers. The trend is away from long periods of curtailment and toward early activity within the limits during which co-ordinated motion can be done. Early activity is important in the development of the musculature. The activities of patients are often curtailed because it is thought that fatigue will produce further weakness. However, the danger of development of undesirable patterns of motion, through lack of co-ordination produced by too strenuous exercise, is probably of greater importance than the factor involved in fatigue.

When activity is increased, care should be taken to use supports of various kinds to hold weakened and paralyzed parts in positions which will not encourage substitutionary movement and which will enhance the development of co-ordinated action. Appliances which will allow activity without danger of producing deformity and poor muscular control should be used early. There is a belief that appliances, such as braces, corsets, and splints, are not necessary or that they hinder ultimate recovery. It appears illogical to curtail the activity of a patient for long periods when appliances may allow him to become active without danger of producing deformities or muscular imbalance. Likewise it should not be assumed that if a patient can accomplish certain activities, for example, walking without braces when both legs are paralyzed, deformities may not develop in later years. Furthermore, in such instances instability may curtail his activities to such an extent that the inconvenience of wearing braces may be overshadowed.

In training the patient who has extensive poliomyelitis it is necessary to bear in mind that in addition to trying to increase muscular strength and produce the best possible function of the remaining muscles, the patient must be physically rehabilitated to the greatest possible degree.

If, after a reasonable period, severe paralysis and weakness persist and recovery seems to have ceased, efforts should be directed toward the development of the remaining muscles and the use of various permanent supports. More time should be spent in teaching the patient to handle himself with what he has than in continuing to re-educate muscles which show no signs of recovery.

The patient is taught to walk, get in and out of chairs, step up onto and down from curbs, climb stairs and develop endurance to such an extent that he may have independent locomotion for a considerable time without rest. In most instances it is not necessary to wait months before this stage

of the treatment is started; it should be started as needed from the time the patient becomes active. Frequently patients are given extensive treatment in the form of hot packs, re-education and training, and then allowed to return home, having had little or no training relative to handling themselves independently. Frequently little or no guidance is given to the patient relative to his future life. This is left to the family or to social agencies. These patients must be treated as a whole the same as any severely handicapped patient and the treatment can be considered a partial failure if this is not done. Families in most instances cannot adequately finish the rehabilitation of the patient.

The final stages of treatment consist of the use of permanent orthopedic appliances and surgical procedures for the purpose of correcting deformities and producing stabilization. The stage of recovery in which these may be indicated is probably reached earlier with the present treatment than formerly. It is evident that the treatment of poliomyelitis is still in the stage of inadequacy. However, it is apparent that the disabilities and deformities caused by the disease are not quite as severe as they were formerly.

PHYSICAL MEDICINE IN THE HOME TREATMENT OF ARTHRITIS*

H. WORLEY KENDALL, HOWARD F. POLLEY AND FRANK H. KRUSEN

Adequate treatment of arthritis necessitates the use of physical medicine. The employment of physical medicine in the home treatment of arthritis constitutes a major part of the treatment of the arthritic patient.

Physical medicine may be used in the hospital or clinic by trained personnel and in the home under professional supervision. In most cases of arthritis, home treatment with physical measures finds a place, either as a less elaborate continuation of the beneficial measures carried out in a department of physical medicine by trained personnel or as a primary home regimen of simple physical measures. Because of the chronicity of the more common types of arthritis, a plan has been developed and employed for many years at the Mayo Clinic for encouraging arthritic patients to carry out a simple therapeutic regimen in the home under supervision of their physicians. Physical medicine helps to achieve the following objectives: (1) prevent or lessen deformity, (2) relieve symptoms and (3) shorten the duration of the disease.

There are many ways of utilizing each of the essential physical measures. The proper management of the various types of arthritis requires careful diversification of therapeutic measures. It is important that the arthritis in each case be considered from the standpoint of causation, type, severity, duration, joints involved and expected results and that an individualized

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program should be planned. While physical treatment plays an extremely important part in the control of many types of arthritis, it should never be used to the exclusion of other procedures. The five main groups of physical measures employed are: (1) thermal measures, (2) massage, (3) therapeutic exercise, including general postural training, (4) graded occupational therapy and (5) adjuncts such as rest, manipulation, traction, splints and supports.

THERMAL MEASURES

Local heating of one or more involved joints may be done best with a simple homemade baker or so-called clamp lamp. Both are relatively inexpensive. The homemade baker consists of a polished, slightly curved, roof-like reflector on supporting legs. The baker is 19 inches (48.26 cm.) long, 19 inches wide and 16 inches (40.64 cm.) high. The frame supports are iron rods $\frac{1}{2}$ inch (1.27 cm.) in diameter. Two double receptacles are attached under this tunnel-like reflector, which covers the part to be treated. Four 60 watt carbon or tungsten filament bulbs are placed in the double receptacles to supply the luminous heat. If a lamp is used, a carbon filament, tungsten filament or tungsten CX type bulb is fitted in a cup-shaped reflector (0 to 10 inches [15.2 to 25.4 cm.] in diameter at its greatest circumference) and either attached to a stand or to a clamp that may be fastened easily to the back of a chair. The base of the reflector is then placed 18 to 20 inches (45.7 to 50.8 cm.) from the surface to be treated. A thirty minute application with either the lamp or baker is usually sufficient for one period of treatment. The use of these luminous heaters is preferred to the use of a common electric heating pad. The latter often becomes too hot for proper local treatment and we also have discouraged its use because of the danger of burns.

Physicians are occasionally faced with the problem of prescribing a method of local heating for patients who do not have electricity in their homes. The use of ordinary paraffin wax for local applications of heat has proved very satisfactory. The patient is instructed to fill the outer container of a double boiler with water and place the paraffin wax in the inner container. The paraffin is then heated to the melting point and allowed to cool until a thin film has formed on the surface. At this time, when the paraffin is at its low melting point, the temperature will be just tolerable to the human skin. Paraffin may then be painted over the involved joint with an ordinary paint brush or smooth wooden handle wrapped in gauze or linen, or if an extremity is being treated it can be dipped momentarily in the paraffin bath. About a dozen coats of paraffin are applied in rapid succession until a thickness of $\frac{1}{8}$ to $\frac{1}{2}$ inch (0.3 to 0.6 cm.) is obtained. The paraffin is allowed to remain on the area to be treated for thirty minutes to an hour. Paraffin should never be applied over hairy skin without preliminary oiling or shaving of the part to be treated. On wrists, ankles or knees, it is sometimes advisable to use a dressing of paraffin and gauze. The technic is simple and as follows: First, a layer of paraffin is painted around the joint; next, a few turns of gauze are applied to cover the first layer of paraffin; then successive layers of gauze and paraffin are applied until a thick firm dressing surrounds the joint. Such a dressing will retain its heat for approximately one hour; a dressing may be left on for twenty-

four hours to provide a temporary firm support for the joint. It then should be removed in order that massage and exercise may be administered prior to application of a similar dressing.

The contrast bath or alternate local applications of heat and cold frequently are of benefit for patients with arthritis, particularly of the hands and feet. These applications may also be employed as a nonelectric method for production of local hyperemia. For best results, the hot water is kept at a temperature of approximately 105° to 110° F. and the cold water at about 50° to 60° F. Studies of the cutaneous temperatures by Woodmansey, Collins and Ernst and by Martin and his associates have resulted in changes in the time used for alternating the immersion of the extremity in hot and cold water and the total duration of the treatment. We first place the extremity to be treated in the hot water for a period of ten minutes, after which the extremity is immersed alternately for one minute in the cold water and then for four minutes in the hot water. This treatment is continued for a total period of thirty minutes once or twice daily. It is always important to start and end with immersion in the hot water. In our opinion, the initial heating for ten minutes hastens the attainment of maximal vasodilatation.

Insufficient attention has been paid to the use of certain physical measures for systemic heating in the treatment of arthritis. Hot tub baths taken by the patient in his own bathtub may be of considerable value in increasing the peripheral circulation and the general metabolism. The temperature of the water may range from 100° to 104° F. and the duration of treatment may be between twenty and thirty minutes. For asthenic and emaciated patients, the lower temperatures and shorter periods of time should be used at the beginning.

The whirlpool bath may frequently be used to advantage in the treatment of arthritis involving the joints of the extremities. A whirlpool bath may be made for home use and may be found valuable in helping to overcome deformities. The part to be treated is placed in a bath of whirling, aerated water at a maximal temperature of 110° F. for thirty to forty-five minutes. Such a bath produces great dilatation of peripheral capillaries, a soothing effect on the peripheral nerve endings and aids in the relaxation of the muscles.

The full wet pack may also be used to advantage in treatment of arthritis in the home. The directions for the use of this pack are as follows: Spread a rubber sheet over the bed and a blanket over the rubber sheeting. Immerse a cotton sheet in hot water (110° to 115° F.) and immediately wring it out. Open the sheet and spread it over the blanket. The patient then lies flat on his back on this warm, moist sheet. He is then instructed to raise his arms above his head. Fold half of the sheet closely over the patient's body and high under his arms. The patient then lowers his arms to his sides. The remaining half of the wet sheet is wrapped around the patient with the upper edge surrounding the neck. Press a fold down between the legs and feet and fold the lower end under the heels. The blanket then is smoothly folded around the patient and an extra blanket is added on top. Hot water bottles properly covered may be applied to the feet. The pack should be applied rapidly and may be used for periods of forty-five minutes to one hour once daily.

MASSAGE

Massage should be employed immediately following the use of heat. It is applied to the soft tissues adjacent to involved joints. One may gradually increase the intensity of stroking and kneading of the muscles around the joint in an attempt to improve the circulation and tone of the muscles. Massage should be modified if there is acute pain on movement of the involved joint and should not be used if there is a rise in cutaneous temperature in the region of the joint. We have found that it is possible for a skilled technician to instruct a member of the patient's family in a few simple massage strokes which can be carried out advantageously as part of the home treatment.

THERAPEUTIC EXERCISE

Therapeutic exercise is usually performed immediately following the massage, during the period of continuing hyperemia. Exercise should be graduated from passive to active assistive, and, finally to active voluntary motion. Passive exercise is usually accomplished by the technician without effort or resistance on the part of the patient. It is used to retain as much movement of the joint as possible during acute inflammatory stages. Active assistive exercise is generally used to obtain increased motion of the joints and to assist in re-educating and strengthening muscles to a point where active voluntary exercise can be done. It is possible to manipulate arthritic joints gently without anesthesia by means of active assistive exercise. The patient makes an active effort to move the joint as nearly as possible through its fullest range of motion and is assisted by the operator in carrying the movement beyond this point. Active exercise means free exercise which can be performed by the muscle without the aid of external forces. This should be started as soon as possible to help maintain normal or useful range of motion of the joints. Joints of the lower extremities should be exercised while the patient is in either a supine or sitting position before exercise is attempted under the strain of weight bearing. Special attention should be directed toward exercises for the feet.

Underwater exercises may be of value as movements often can be carried through a greater range with less pain under water and, because of the buoyancy of the water, weakened muscles are capable of greater amounts of work. Therapeutic exercise should be slow and rhythmic and through the fullest range of motion that is relatively painless. One should always avoid jerking, wiggling and pump-handle movements. One slow daily movement through the fullest possible range of motion in each direction is preferable to many minor movements through a partial range of motion.

Postural exercises properly applied help to balance the body so that there is an optimal alignment of joints and avoidance of strain. It has also been stated that postural exercises tend to promote normal visceral function. The patient who has faulty posture should attempt to follow five cardinal rules for assuming and maintaining correct posture: (1) standing and walking with the feet pointed straight ahead and with the weight evenly distributed; (2) rolling the hips under (contracting the gluteal muscles downward and the abdominal muscles upward, thus rotating the pelvis to a more level position); (3) raising the chest; (4) lifting the back part of the head toward the ceiling (thus straightening the thoracic and cervical

segments of the vertebral column); and (5) walking, standing and sitting as erectly as possible.

OCCUPATIONAL THERAPY

A skilled occupational therapist should be consulted in planning for this type of home therapy. Often the patient can use occupational therapy for increasing the activity and usefulness of the involved joints. Many patients have found occupational therapy a source of remuneration, particularly when they have been prohibited from returning to their previous occupations. For exercise of the knee, hip or ankle, one may employ a velocipede or a stationary bicycle. For mobilizing the ankle, one may utilize a foot-pedal sewing machine. For exercising stiff fingers and wrist, modeling with clay or hammering and planing are of value. For exercising the shoulder, elbow and upper part of the back, suitable exercises may be provided by having the patient do basketmaking or loom weaving with the material placed on a table or bench high enough to require him to increase the range of shoulder motion as he works.

ADJUNCTS

Rest.—Rest, if judiciously prescribed, is a valuable therapeutic measure in the treatment of arthritis. However, it must be kept in mind at all times that atrophy of the muscles, periarticular tissues, bone and skin results from prolonged rest and must be avoided if possible. During acute and subacute stages of the disease, more rest may be needed than in the later stages when the disease is less active. The amount of rest for each patient should be modified from a basic minimum of ten hours in bed at night and one hour of rest each morning and afternoon. The patient is advised to avoid general fatigue rather than to remain at absolute rest. The patient also should be warned against injuring the joint by unnecessary weight bearing or other activity, and should be instructed to avoid irritation from repeated aimless movements of the involved joints. In so far as possible, he should avoid hurry and, particularly, worry, and at the same time he should take enough nonfatiguing exercise to improve posture and to maintain proper mobilization and alignment of the joint.

Manipulation.—Manipulation performed by skilled hands while the patient is anesthetized may be a powerful weapon in improvement of function in selected cases of rheumatoid and traumatic arthritis. However, such a procedure requires more experience than probably any other type of orthopedic procedure. The joints which respond particularly well to manipulation are those of the shoulder, hip, knee and ankle. It is highly important to begin active assistive exercise within twenty-four hours after manipulation under anesthesia in order that the mobilization obtained by manipulation may be maintained. In our opinion, it is far better to give an analgesic or narcotic and exercise the joint early after manipulation than it is to allow the joint to remain immobile until motion is more difficult to obtain. After manipulation under anesthesia, the patient should be kept under close observation until improvement becomes sufficient to warrant undertaking a definite program of home treatment.

Traction.—The use of traction and rotation of the cervical portion of the spinal column has proved helpful in relieving the radiculitis secondary to

osteo-arthritis of this portion of the spinal column. Radicular pain of this type is usually localized in the shoulder girdle, arm or pectoral region. If cervical traction and manual rotation in the Sayre type of head sling produce relief from the radicular pain, the patient often can continue the procedure by using a simple head sling at home. Needless to say, careful selection of patients for this procedure is of paramount importance.

Splints and Supports.—The proper fitting and application of splints, shoes and other supports aid in prevention and correction of deformities. These devices frequently are of major importance in the treatment of rheumatoid arthritis, especially when weight-bearing joints are involved. Use of elastic supports for the knee or ankle during weight-bearing activity are frequently of value. The proper fitting of shoes and supports often will make it possible for the patient to walk more correctly and thus permit an adequate amount of active exercise with minimal trauma to affected joints. A well-constructed and properly fitting oxford type of shoe is usually advised. The heel should have a level surface, at least $\frac{1}{2}$ square inches (25.8 sq. cm.) of standing surface, and should be not more than 2 inches (5 cm.) in height. Sometimes the shoes should be equipped with a transverse metatarsal bar on the sole just posterior to the transverse arch of the foot, a soft felt pad to support the longitudinal arch of the foot and occasionally heel pads or wedges. Rigid metal arch supports are not favored because they tend to produce atrophy of the plantar muscles. Use of bedroom slippers and inadequately supporting shoes should be condemned as they may exaggerate deformities in many cases.

The use of a bed which does not sag and the discarding of all pillows, to permit full extension of all joints during regular periods each day, are important. It is well to emphasize that the constant use of pillows under the knees should be avoided because this is one of the most frequently encountered factors in the development of flexion contractures of the knees.

COMMENT

The successful continuation of a home treatment program is dependent on several factors. We believe it is most helpful if the patient understands the manifestations of the disease in his case, the problems associated with treatment of the joints which may be affected and the results to be expected from treatment.

A physiatrist* in the Section on Physical Medicine then prescribes an individualized physical therapeutic program for each patient. The patient is familiarized with the details of his program by one and preferably two or more instruction treatments which are carried out by a trained technician under the supervision of the physiatrist. Detailed instructions written in simple language are also provided. These describe the type and technic of the treatment which has been carried out and help the patient to proceed with the program of treatment in his home. The instructions also serve the additional purpose of acquainting trained technicians in his locality, to whom he may be referred by his home physician, with the program which was initially prescribed.

It is recommended that whenever possible the patient should supple-

* Term recently sponsored by the Council on Physical Medicine of the American Medical Association to describe a physician who specializes in physical medicine.

ment the home treatment with professional physical therapy at least once or twice a week. If control of the arthritis is not satisfactorily accomplished, periods of several weeks or more of intensive treatment in specially staffed and equipped institutions should be considered.

When the patient's local physician is familiar with the prescribed regimen, he can be of valuable assistance in helping to guide the patient's treatment. Consultations between the physiatrist who has prescribed the home treatment and the patient's local physician help to insure continuity and necessary adjustments of the physical medicine program. Real and lasting benefits can usually be expected to result from conscientiously following such a plan.

Follow-up Study of the Results of Home Treatment.—The effectiveness of such a program of treatment was investigated in a recent survey made by Treusch and one of us (Krusen). A follow-up study was made of 218 arthritic patients for whom a program of home physical therapy had been prescribed. It was found that 93 per cent of the patients had continued the prescribed treatment for varying lengths of time at home. Of these, 65 per cent had continued for three months or longer and 27 per cent carried on the home treatment for one year or more. In approximately four of every five cases, patients thought they were benefited by the use of the physical medical program employed for home treatment. It was also noted that all of the patients who had rheumatoid arthritis were continuing a regular program of treatment and that 88 per cent of these patients were being benefited. The impression was also obtained by this survey that the patients who received two or more instructional treatments were more likely to continue on the regimen at home than were those who had received only one instructional treatment.

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ANESTHESIA AND GAS THERAPY

ADVANCES IN ANESTHESIA*

JOHN S. LUNDY

Advances in anesthesia follow several lines of endeavor. I shall try briefly to mention some of them. For example, the most notable situation in history exists today in the fact of the great latitude in choice of agents and methods. In nitrous oxide one has a mild, quick-acting analgesic agent associated with a short period of recovery and relative safety in respect to fire and explosion hazards. This agent is generally available, and is used rather skillfully by a large number of individuals. Ethylene similarly is generally available, and although the fire and explosion hazard which attends it has limited its use, it is still one of the outstanding agents from the standpoint of safety in the anesthetization of patients suffering from shock or heart disease. Cyclopropane is potent and is accorded widespread use. It is not free of hazard from fire and explosion, but it is capable of producing better relaxation than are any of the other gases. The period of induction is short. The occasional difficulty encountered when an untoward result is observed just as the anesthesia has been terminated is not fully understood, but apparently it is peculiar to certain technics of the administration of cyclopropane. I refer to the so-called cyclopropane shock that is seen at the termination of anesthesia in an occasional case.

The devices with which the gases are administered have not been improved for many years, and probably will not be until adequate mechanisms for the analysis of the atmospheres within the breathing bag and various parts of the machine are developed. I think that it is safe to say that this advance can be anticipated either this year or next year.

Of the several types of ether that have been developed, none seems to be better than diethyl ether. In this centenary year of the use of chloroform it is interesting to notice that anesthesia produced with this agent still is fraught with danger, and yet chloroform has certain qualities which make it an agent tempting to many, and reports on its use from time to time are still given. It would seem that the favor originally accorded chloroform might have been more prolonged had it not been for the introduction of so many good agents in the last few years. Another agent is ethyl chloride. Very few reports concerning this agent are seen now, probably because, like chloroform, it is not generally used.

In the field of local anesthesia various agents have been introduced such as nupercaine, pontocaine and others. These agents seemed to be required because prolonged anesthesia could not be maintained with a single dose of procaine hydrochloride. This was especially true in block and spinal anes-

* Submitted to Surgery.

thetia. Lemmon's introduction of continuous spinal anesthesia was followed by Tuohy's modification of Lemmon's method, which was in general an adaptation of Adams' technic for the production of continuous caudal anesthesia. That is, by use of a catheter instead of a needle, it became possible to produce anesthesia of desired length with procaine hydrochloride. This was important because I believe procaine hydrochloride is the safest available agent for local anesthesia. Here is an instance in which improvement in technic has greatly increased the efficiency of an old agent, and it is an outstanding advance in anesthesia whenever that result can be obtained.

The introduction of the Magill intratracheal tube was without doubt a great advance in inhalation anesthesia. This technic is used extensively to great advantage now in many types of surgery. For intracranial operations it has made the patient's breathing quiet and has obviated the increased intracranial pressure which often occurred when an anesthetic agent such as ether was administered for this sort of operation. Use of the intratracheal tube in plastic surgery is essential so that the surgeon may have the operative field to himself and so that it may be kept sterile. One of the most important applications of the intratracheal tube is in thoracic surgery, where it permits the lungs to be inflated at will during the operation, with the thorax opened. In abdominal surgery the quietness of respiration which the technic ensures is desirable, and the ease with which the anesthetic agent can be introduced into the lungs and from there into the blood stream and thence to the nervous system has increased the efficacy of inhalation anesthesia generally. The Magill technic is especially valuable when an operation is to be performed on a patient's back and he must be placed in the prone position. In all the operations mentioned, and with all the various anesthetic agents suited to the technic, it is possible, with the tube in place, to aspirate material from the trachea and bronchial tree both during anesthesia and for a short period afterward. This decreases morbidity and mortality rates considerably.

Intravenous anesthesia gradually has won widespread favor largely because of pentothal sodium. It is generally recognized that administration of this agent should be preceded by preliminary medication, usually with a barbiturate and morphine and atropine. The dose of pentothal sodium should be kept relatively small; that is, usually it should not be more than 1 or 2 gm. for a patient. It is definitely understood that solutions for pentothal sodium stronger than 2.5 per cent are hazardous. In combining nitrous oxide and oxygen (50 per cent of each) and using this mixture in association with pentothal sodium, we are *able definitely to reduce the amount of pentothal sodium that otherwise would be administered.* The administration of small quantities of pentothal sodium to induce anesthesia before inhalation anesthesia is begun has been much appreciated by patients. The *technical point of importance in this connection is that not more than 10 c.c. of a 2.5 per cent solution of pentothal sodium should be administered before inhalation anesthesia is begun, and it is better if the amount can be kept to 6 or 7 c.c.* Larger amounts of pentothal sodium interfere with the depth of respiration, and therefore interfere with production of the desired result with the inhalation anesthetic agent. A second technical point in the use of pentothal sodium is that if the effect of the preliminary medication

on the patient is minimal and if, when 10 or 15 c.c. of a 2.5 per cent solution of pentothal sodium has been administered within a few minutes, satisfactory anesthesia is not obtained, then an additional dose of morphine should be injected intravenously. This additional dose usually should be $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.008 to 0.01 gm.).

Nevertheless, it is realized that pentothal sodium does not provide every thing that might be desired in an intravenous anesthetic agent. Therefore, further investigations have been made for new agents, or suggestions have been advanced that something might be combined with pentothal sodium to give it the potency which it lacks.

The question of relaxation of the patient is of prime importance to both surgeon and anesthesiologist. The advent, then, of curare in medical practice, especially in connection with the administration of anesthetic agents, has made a great impression on those who have used it. Curare produces excellent relaxation, with relatively little postoperative prostration. It has been used most commonly in association with cyclopropane anesthesia, in which relatively large quantities of oxygen are used. Curare and cyclopropane, especially when an intratracheal tube is used to administer the anesthetic agent, give a result that is highly desirable in most instances. The great impression caused by this particular combination stimulated the use of curare with nitrous oxide, ethylene and also other anesthetic agents. In the latter instance less curare is required than when curare is used with the gases. The use of curare with pentothal sodium has been tried repeatedly; in such a combination curare does give a degree of relaxation that pentothal sodium in itself cannot provide. Recently, Baird suggested the use of pentothal sodium plus curare, the curare preferably having the form of a solution of d-tubocurarine chloride. Baird was greatly impressed with the results of administration of these agents in combination in one syringe, the mixture being 1 mg. of d-tubocurarine chloride per cubic centimeter of 2.5 per cent solution of pentothal sodium. At the same time, oxygen or nitrous oxide and oxygen is administered to keep the patient oxygenated.

In this respect, we ought not to forget that the anesthesiologist's understanding and actual use of stimulants and supportive measures are hardly less important than the method of anesthesia employed, whatever it may be. This is a consideration of the utmost significance which serves to emphasize the need for extension of the period of the anesthesiologist's training, to which I shall advert later.

As we look back and examine the present and speculate as to the future, it would appear that the status of anesthesia now is relatively good and that apparently it will improve. This opinion is based strictly on the agents available now and on those which it is possible to envisage. An additional important phase, however, of the present status of anesthesia is that more and more physicians have interested themselves in the field of anesthesiology. A number of institutions have established either temporary or fully approved residencies in this specialty, and in some instances prominent anesthesiologists may teach by the preceptor method. There are a national society of anethetists, a certifying board for proficiency in the specialty and a section of the American Medical Association, all actively devoted to the advancement of this field. The demand for skilled physician anesthesiologists exceeds the supply, and no doubt will continue to do so for some

In 1942 the idea of a postanesthesia observation room was inaugurated. This idea differed definitely from that of the old surgical recovery period in that the patient was sent to this room for reasons associated only with anesthesia in the majority of cases. The room was staffed by persons experienced in caring for patients who were recovering from general anesthesia; adequate equipment and supplies, including oxygen, carbon dioxide and so forth, were present to support the patient's pulmonary ventilation; also available were the supplies used in parenteral therapy for support of the patient. This had a definite effect on the surgical department in that the assistant who went with the patient to this room was able to return immediately to the operating room for the next operation, leaving the intravenous and subcutaneous administration of fluids to the personnel from the anesthesia department. The patient's condition, if it were not satisfactory, could be checked by the physician anesthetist in charge; this physician then became a standard part of the surgical team and assumed some of the responsibilities previously borne by the surgical team, that is, he was expected to give the patient protection until such time as the patient could be turned over to the care of the surgical team free from the effects of anesthesia. It gave the anesthetist additional responsibility which could not be supplied by a nonmedical person and in many ways it seemed to increase the cost of anesthesia. Again this increased cost proved its value in that the patient generally was better anesthetized, that is, he was at least more safely anesthetized with relaxation being produced with relative safety; preoperative examination of patients was made with medical judgment and preliminary medication that was suitable was ordered so that it augmented rather than frustrated the efforts of the anesthetist; and the supportive therapy was in general managed by the anesthetist and was given from the relatively same medical point of view as though it had been handled by one whose training definitely was surgical. In the postoperative period those incidences of morbidity that presented themselves were given medical attention by the anesthetist and in a short period of time it was shown that postoperative pulmonary complications, and particularly cardiovascular complications, were more satisfactorily handled than ever before.

In general it appears that the advances in anesthesia are not limited to the introduction of new agents and methods, as important as those contributions are. There has been a marked change as a result of the shifting of responsibilities and activities to a medical level. This is not to say that there have been no good nurse anesthetists. There have been many who have satisfied their surgeons and who have demonstrated real ability in the administration of anesthetic agents. However, even they would not care to be charged with the medical responsibility which is now involved in the administration of the anesthetic agents, the support of the patient and the expediting of operating procedures. The department of anesthesia in large hospitals and in many small ones has changed considerably in respect to the type of personnel employed. The minimal facilities that most institutions are satisfied with are a well-trained physician anesthesiologist who will supervise this whole indicated procedure day after day; thus the best he can do is to surround himself with the best available personnel, hoping that he can give competent coverage twenty-four hours a day and seven days

a week; this, in turn, means that an increase in personnel, especially in medical personnel is necessary. All this has a definite effect on the surgical department in that the anesthesia department has become very much more expensive and the patient must bear largely this increased burden. Under these circumstances the superintendent of the hospital who previously had been tempted to support the hospital generally with profits from a less complicated anesthesia department finds himself in a position in which he prefers to give the patient the advantages of present day facilities and advances in anesthesia with the expectation that a more rapid turnover of patients will tend to cause the income to be increased at least sufficiently to offset the increased cost of the anesthesia department. The financial benefit to the hospital under the old plan for anesthesia is less important, I believe, than the many benefits that can be exhibited under the new plan, with the many improvements in agents, technics and type of personnel employed

METHODS FOR MAINTAINING BLOOD PRESSURE*

JOHN S. LUNDY

The most recent method of controlling blood pressure is that of Page. The 15 gauge needle inserted into an artery (radial) allows blood to be withdrawn rapidly enough so that it may be citrated without clotting. Arterial blood pressure may be reduced by the withdrawal of 750 to 1,000 c.c. of blood and as soon as the operative field is satisfactory for the surgical procedure further blood need not be withdrawn. If pressure falls too low blood may be returned to the vascular bed, either through the artery or through the vein. The indications for employment of this technic are not clear in all types of surgery but have been applied satisfactorily in certain operations on the brain in which severe bleeding occurs.

In most surgical operations one of four plans may be adopted. The first, and most foolproof, plan is that of inserting a 15 gauge needle into a vein after anesthesia has been induced and, before the operation starts, beginning the slow administration of a solution of dextrose, 5 per cent in isotonic saline solution or dextrose, 5 per cent in water. The second best method is that of inserting a 15 gauge stilette needle into a vein in anticipation of the employment of parenteral therapy. A third, and less desirable, method is for the anesthetist to follow the patient's blood pressure until some evidence of impending shock is observed and at that time to insert the needle and begin the administration of fluids. A fourth, and still less desirable, method is to wait until evidence of shock presents itself, to attempt to combat this with stimulants and, after failure to accomplish the desired result, then to attempt the venipuncture and administration of fluids.

I shall discuss only the first method. Most patients, unless they are admitted for emergency treatment, come to the operating room after hav-

*Abridgment of paper read at the Joint Meeting of the American Society of Anesthesiologists and the Ohio Society of Anesthesiologists, Cleveland, Ohio, October 4, 1917.

ing been on a restricted diet and fluid intake. Five per cent solution of dextrose in water is probably preferable in cool weather and 5 per cent dextrose in isotonic saline solution in hot weather. The opinion is based on loss of salt in hot weather. As the operation and anesthesia are continued, if blood pressure and pulse rate indicate impending shock the rapid administration—which is best done through the large gauge needle—of 100 to 250 c.c. of fluid is the quickest method I know of to decide the degree of shock that is present. If the patient's blood pressure rises 10 to 15 mm. of mercury the quick administration of fluids and the rate of dripping of the fluid may be slowed and the patient watched. The patient's condition should be checked frequently to see that pressure is maintained.

If, on the administration of the 100 to 250 c.c. of fluid rather quickly—that is, in less than five minutes—pressure does not increase at all then one should resort to blood transfusion immediately. One should be governed somewhat in this regard by the amount of blood that the patient has lost. It is not necessary to have a device for measuring blood loss to see that the patient has lost only 100 to 200 c.c. of blood, or that he has lost 500 or 1,000 c.c. of blood. The escaped blood is evident to the surgical team. When blood loss can be measured—in some operations it can be—one may know almost exactly how much blood needs to be administered. However, for adults the amount of blood transfused is usually not less than 500 c.c. It may be two or three times this amount, or whatever is necessary to bring the blood pressure to a set level, keeping in mind the preoperative level of blood pressure of the patient, which if low or high will, to some extent, determine the amount of blood to be administered. When blood has been lost I believe that for transfusion there is no substitute for blood. For patients who have been severely burned, plasma is obviously of value. But here again a blood transfusion may also be needed.

In routine cases when time permits it is considered the technic of choice to determine the patient's blood group and Rh factor, to use blood from a donor of the corresponding group and Rh factor and to cross match the blood. However, cross matching is not often done before operation and frequently time does not permit its being done during the operation, so that for the most part, it is generally satisfactory to the anesthetist if the patient's blood group and his Rh factor have been determined and if blood of corresponding group and Rh factor can be made available quickly.

The rate of administration of blood is determined by the response of the patient's blood pressure. I have administered as much as 2,200 c.c. of blood in twenty-two minutes in order to combat protracted and massive hemorrhage. I know of no instance in a surgical case where the rapid administration of blood has been harmful, provided that the blood pressure was low when the administration was begun and that the rate of flow was slowed to less than 100 drops a minute. It is always possible, when blood pressure falls during administration of fluids and there is some delay in obtaining blood, to mix a blood pressure-raising drug, such as ephedrine, desoxy-ephedrine (desoxyn) or phenylephrine hydrochloride (neosynephrin hydrochloride), so that the patient will receive a stimulant along with the fluids. This sometimes gives a better regulation of blood pressure than the sudden administration of one of these stimulants in a more concentrated form, although it is more the custom to give the stimulant in concentrated

form than to give it in diluted form. Either way will help to support the patient's blood pressure for ten to fifteen minutes until blood can be obtained.

Plasma, widely used during the war, has not proved itself to be entirely satisfactory as a supportive agent. Many efforts have been made to find a substitute for plasma. Acacia in isotonic saline solution has been used with some success, as well as solutions such as gelatin in large molecular weight and ichthyocolla (isinglass). Recently, I was told by Weese, of Germany, that he has had remarkable success with kollidon (polyvinylpyrrolidon). One of the most recent and interesting developments has been the use of dextran. This substance tends to stay in the circulation for some hours. It is, therefore, very useful to the anesthetist. In a high percentage of unanesthetized patients an anaphylactic type of reaction to the material has developed. The preparation of dextran which I have used in about 500 cases now has been designated as *macrose*. It is a 6 per cent solution of dextran in isotonic saline solution. The use of this agent in supporting blood pressure during a Smithwick operation for hypertension has been very satisfactory. The combination of this material with a stimulant drug such as ephedrine or neosynephrin hydrochloride seems to be actually and theoretically more certain of maintaining blood pressure than when solutions of materials of smaller molecular weight are employed. However, *macrose* is not a substitute for large amounts of blood that have been lost. One must always be prepared to resort to the use of blood when its replacement is necessary.

INTRAVENOUS ANESTHESIA*

R CHARLES ADAMS

The principles underlying the intravenous use of a general anesthetic agent are sound. If we can by-pass the respiratory tree by injecting the anesthetic agent directly into the blood stream, we can circumvent some of the difficulties associated with inhalation anesthesia. The factors that may prevent an agent from reaching the pulmonary circulation—voluntary and reflex breath holding, mechanical obstruction, depression by preliminary medicaments and those resulting from a defective absorptive mechanism in the alveoli—may not be the same problems when the intravenous route is employed. In intravenous anesthesia there is less tendency toward the production of mucus, since irritation of the mucous membrane is less. Nausea and vomiting, which result in part from the swallowing of the anesthetic agent, are definitely decreased.

Pentothal sodium anesthesia now has been used for twelve years. During this short period it has been aligned, in importance and in frequency of use, with inhalation and regional methods. Is its present lofty position in the field of anesthesiology justified? This may be answered in two ways: as a total anesthetic agent, no; as an important integrating and supplementing

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agent, definitely yes. The future of the method rests for the most part on its value as a supplementary agent, and as such it has a multitude of uses. Fortunately, pentothal sodium is compatible with most of the anesthetic agents. It can be used with any of the gases or ether, and is outstanding as a supplement to local, regional and spinal anesthesia.

Perhaps one of the most important uses of pentothal sodium has been to provide anesthetic combinations which are thoroughly free from the hazards of fire and explosion, and which permit the use of all types of electrosurgical instruments. Nitrous oxide-oxygen-pentothal combinations, with or without local or regional procedures, will take care of most of these situations.

In the last year or so the use of dilute solutions of pentothal sodium (0.5 to 1 per cent) has been on the increase. The resultant anesthesia is thought to be more smooth and more even when some type of continuous drip method is employed. I feel that the technic in which 2.5 per cent solution is injected is more flexible and controllable and that it requires less attention to details for the short operations in which pentothal sodium is most used, than is true of the continuous drip method.

Large doses of pentothal sodium, whether administered over short or long periods, are potentially hazardous, even though the patient may not appear to react untowardly. Anoxia, as a result of respiratory depression, may not always be apparent in the patient's general appearance.

The presence of hepatic damage in itself is no contraindication to the use of pentothal sodium. However, experimental evidence leads to the assumption that prolonged anesthesia with pentothal sodium interferes, or large doses of this agent interfere, with the glycogenic and glycogenolytic properties of the liver. Since pentothal sodium falls short of producing total anesthesia with safety, it is necessary to continue to think in terms of compensating for this deficiency. The newest combination naturally would be pentothal sodium and curare. The results obtained to date with pentothal sodium and curare have been promising, and the reduction in the amount of pentothal sodium permitted by such a combination has been marked. I hesitate to say whether or not the combination will provide a safe method of anesthesia for abdominal operations. Some are already using it for this purpose. To date, I have used curare with pentothal sodium for the sole purpose of reducing the amount of pentothal sodium required in cases in which we ordinarily would use pentothal sodium alone. Both agents are potent respiratory depressants, and as such must be administered with due caution. Two methods of administration are employed.

In the first method, each agent is injected individually. With this technic anesthesia is induced with pentothal sodium. Curare is then injected in 20 unit or 3 mg. doses at two to four minute intervals, and injection is halted when moderate respiratory depression is produced, regardless of the dose employed. The remainder of the anesthesia is then carried out with pentothal sodium in the usual way.

In the second method the pentothal sodium and curare are mixed in the same syringe. Knight and Baird have worked out a mixture which contains 5 units of intocastrin or 0.75 mg. per cubic centimeter of the mixture. They have used the mixture combined with nitrous oxide and oxygen (50-50) in a variety of cases, including abdominal operations. We have used both this mixture and also solution of d-tubocurarine, the concentration of the latter

drug being 0.70 mg. per cubic centimeter of solution. The results from the use of both preparations with pentothal sodium were comparable.

If an excess of curare is added, a precipitate forms which will redissolve if more pentothal solution is added. Whether or not there is a synergistic action as a result of injection of a mixture of these two drugs I cannot say. Frequently, operations of two hours' duration have been carried out with the use of less than 1 gm. of pentothal sodium. It seems to me that the margin of safety is greater when the drugs are injected separately than it is when they are used together, since patients vary widely in their tolerance of both the barbiturate and curare.

Endotracheal intubation carried out with the patient under the influence of pentothal sodium never has been very satisfactory. The addition of curare has greatly increased the ease of introduction of the tube. One other advantage of use of the combination is the resulting lessened incidence of laryngospasm, which is often so troublesome when pentothal sodium is used alone.

THE GENERAL PROBLEM OF ANESTHESIA IN OBSTETRICS*

EDWARD B. TUOHY

The problem of providing anesthesia to women in childbirth and of performing the safe delivery of newborn infants is a major responsibility, especially for the general practitioner. In hospitals where obstetric facilities are readily available the teamwork between the anesthesiologist and the obstetrician simplifies somewhat the general problem of handling the parturient mother.

There are certain factors which should be considered in the choice of any general or local anesthetic, analgesic or amnesic agent. They are as follows: 1. What is the physiopharmacologic action of the agent on both maternal and fetal structures? 2. What fetal or maternal diseases or abnormalities exist which may alter the selection of certain agents? 3. What agent or agents and method are best suited to the emotional and physical status of the mother? 4. Is the method used one which will afford the greatest safety to the mother and the infant? Certain criteria should be present in the choice of any agent or method. These agents should possess adequate properties to obtund the pains of labor without any untoward systemic reaction. Secondly, the agent should be reasonably prompt in its action and should not possess cumulative effects. Thirdly, effective means of counteracting an overdose or idiosyncrasy to the agent should be available.

It might be pointed out at this time that the wisdom or advisability of the attempts to relieve the pains of labor totally have been seriously questioned by some authorities on this subject. De Lee and Greenhill have emphasized repeatedly the price that is paid to make childbirth painless. Heaton in writing on obstetric anesthesia and analgesia commented: "Perhaps, as the psychiatrists have suggested, the inordinate demand for pain-

* From *Minnesota Medicine*, 50:955-955 (Sept.) 1917.

less childbirth is symptomatic of the anxiety and insecurity among certain groups in our culture today. It is questionable from a psychologic standpoint whether the passive role assigned to women in painless childbirth is a desirable one."

Opinions of various investigators with respect to the effects of certain agents are occasionally controversial, so that the comments made here are a composite opinion and not one individual's conviction.

Many methods of analgesia and anesthesia have been proposed but some of these are limited in their practical application because they are too technical and complex. Continuous caudal anesthesia might be mentioned as an example of a highly technical procedure which is very valuable but has limited application. In the conduct of the average uncomplicated labor and delivery the obstetrician and the anesthesiologist, singly or together, focus their attention on amnesic, analgesic and anesthetic agents which will obtund pain and produce at least relative amnesia. In the first stage of labor analgesic and amnesic agents are usually sufficient. In the second and third stages of labor anesthetic agents are required, as a rule.

FIRST STAGE OF LABOR—AMNESIC AND ANALGESIC AGENTS

At present scopolamine in conjunction with a barbiturate such as pentobarbital sodium is one of the most effective combinations. The dose of scopolamine is 1/150 or 1/100 grain (0.00043 or 0.00065 gm.) hypodermically administered when labor pains are well established and regular and there is effacement and beginning dilatation of the cervix. Simultaneously 1½ to 3 grains (0.1 to 0.2 gm.) of pentobarbital sodium are given orally. The administration of scopolamine is repeated about one hour after the initial injection. Some authorities recommend three doses of 1/100 grain (0.00065 gm.) of scopolamine alone subcutaneously administered at intervals of half an hour when labor is established. The duration of action of scopolamine is about two hours in the dose mentioned. In prolonged labor additional amounts of scopolamine may be required at intervals of two hours. At least one drawback to this method is the occasional occurrence of extreme excitability and stimulation of the patient, necessitating constant nursing attention.

Another combination of agents which has more analgesic effect as well as amnesic action is the use of scopolamine, barbiturates and demerol. The experience of several investigators has shown that the combination of demerol and scopolamine causes less fetal respiratory depression than scopolamine and demerol plus a barbiturate. A suggested regimen with these agents is the hypodermic injection of 100 mg. of demerol along with 1/150 grain (0.00043 gm.) of scopolamine when the labor pains are strong and regular. If these two agents are not quite sufficient a barbiturate can be given orally or rectally as a supplement. The administration of demerol and scopolamine may be repeated at intervals of three to four hours.

At this point a word should be said about morphine and pantopon. In general, these opiates should not be used within less than two hours from the time of delivery, since they cause fetal respiratory depression, and when a general anesthetic agent follows in sequence the incidence of asphyxia neonatorum is definitely increased. This is particularly true when one is dealing with premature infants.

Rectal analgesia should be mentioned because it is liked by many obstetricians and is a well-accepted method of producing analgesia in labor. Ether in oil (65 per cent ether—35 per cent oil), the original Gwathmey technic, has been modified to include paraldehyde, avertin, chloral hydrate and pentothal sodium as rectal analgesics. The use of intravenous anesthesia is not recommended, as a rule, in labor because of the rapid and concentrated action of the agent on both fetal and maternal respiration.

Of the inhalation anesthetic agents for obstetric analgesia both the volatile agents, such as ether, chloroform and divinyl ether, and gases, such as nitrous oxide, ethylene and cyclopropane, are employed. Whereas various techniques of administration of these agents have been described, including self-administration, they are usually administered during the second stage of labor when anesthesia rather than analgesia is required.

ANALGESIA AND ANESTHESIA IN THE SECOND AND THIRD STAGES OF LABOR

Multiparous women give birth frequently spontaneously without the addition of any agent other than the basal analgesia supplied. In most cases, however, some form of general anesthesia or regional anesthesia is required. Time-honored drop ether and chloroform are used extensively, particularly in deliveries at home. In hospitals where the assistance of an anesthesiologist is available many combinations of agents may be used. During delivery when the presenting part distends the perineum the depth of general anesthesia should be carried to plane 1 or 2 of the third or surgical stage of anesthesia. Uterine contractions are not abolished at this level of anesthesia but such procedures as episiotomy and application of forceps can be done without pain to the patient. Nitrous oxide will usually require the addition of ether vapor to provide safe anesthesia in the second and third stages of labor. One should avoid using any concentrations of nitrous oxide greater than 80 per cent along with 20 per cent oxygen. Cyclopropane and ethylene are best suited for the terminal stages of labor and should be administered carefully by the closed technic.

REGIONAL ANESTHESIA

Many procedures have been and are being used, including pudendal block, transsacral block, paravertebral block, caudal block, local infiltration and low spinal anesthesia. Certain techniques require specific training, skill and experience; others, such as local infiltration and pudendal nerve block, require minimal specialized technic. Tucker and Benaron, Cleland, Lull and Hingson, Lundy and Tovell and others have described their techniques and the merits of these techniques are well established. For example, pudendal nerve block is a successful type of block anesthesia for many obstetric operations, including spontaneous delivery, low forceps application, episiotomy and perineorrhaphy. The contribution of Hingson and his associates has shown that the continuous caudal method has a definite place in obstetric anesthesia. It should be performed only by those persons familiar and sufficiently trained in regional anesthesia to know the indications and contraindications to this method. Caudal anesthesia is applicable chiefly to hospitalized patients. Low spinal or saddle anesthesia with hyperbaric solutions is becoming more and more widely used. Any one of several local

anesthetic agents may be used; for example, procaine hydrochloride or pontocaine hydrochloride. If procaine hydrochloride is used 50 to 75 mg. are dissolved in 2 c.c. of 10 per cent solution of dextrose. After a lumbar puncture at the level of the third and fourth lumbar interspace, this mixture is diluted with an equal volume of spinal fluid and injected slowly. The injection is made with the patient in the sitting position. Anesthesia is established quickly and lasts for one to one and a half hours. Postpartum bleeding is diminished and the babies have little, if any, respiratory or circulatory depression.

CESAREAN SECTION

Cesarean section presents a difficult problem as far as the choice of anesthesia is concerned. What may be best for the mother may not be best for the fetus. Prolonged general anesthesia leads to marked fetal respiratory depression and often to death of the fetus. Improperly controlled spinal anesthesia has led to disastrous results. Local infiltration or block anesthesia of the lower abdominal wall in combination with inhalation anesthesia or intravenous anesthesia at the time the uterus is opened has been advocated by many authors. If the timing of the general anesthetic agent is correct, little, if any, depression of the unborn child occurs. The objection to this procedure by the mother is the main obstacle.

Hingson has advocated continuous caudal anesthesia utilizing posture to advance the anesthesia high enough to permit incision of the abdominal wall above the umbilicus. The continuous spinal technic has offered another method of anesthesia which, if performed carefully, will permit safe and satisfactory results for the mother and child. There is usually less loss of blood in cesarean section with local, caudal or continuous spinal anesthesia than with inhalation anesthesia. Of the inhalation anesthetics, if they alone are used, cyclopropane is best as far as the baby is concerned but resuscitation procedures are much more common in these cases than with regional methods or combinations of regional and general methods.

ANESTHESIA IN COMPLICATIONS OF PREGNANCY

Several outstanding complications are noteworthy; namely, (1) hypertensive cardiac disease, (2) nephritis, (3) preeclampsia and eclampsia, (4) pernicious anemia, (5) leukemia and (6) other blood dyscrasias, including hemorrhagic diathesis. In the presence of these complications local or regional anesthesia is to be preferred to general anesthesia, particularly with ether, chloroform or avertin.

CONCLUSIONS

If I may quote from an anonymous editorial, "The obtundation of pain and discomfort incidental to parturition must necessarily occupy a secondary role in most obstetrical deliveries. It does not follow, however, that the pains during labor and delivery usually do not belong in the same category as pain associated with disease or that caused by surgical operation. Labor is not a disease and expulsion of the fetus is not always a surgical operation. They usually constitute a physiologic process.

"The medical profession and its scientific allies have not ignored the pangs of the parturient. In fact efforts have been so generous at times that

pain relief seems to be exalted from its secondary role in obstetrics to a place equalling the more essential functions of the accouchement.

"During all the anesthesia years every new drug or method introduced to facilitate surgery or allay pain has found its way into obstetric practice. The use of ether and chloroform during childbirth had a formidable place in early controversies surrounding the acceptance of anesthesia but the drugs have played an important role in obstetrics since. The lay press and non-medical benefactors formulated and expressed opinions on the merits of the early pain relieving procedures. They have followed through with similar journalistic efforts with the advent of every new departure. Not infrequently obstetricians have resented the publicity and particularly the inaccuracies published for public edification. Their remonstrances have led the modern accredited press to more conducive reporting based upon statements that may claim authority. However, enthusiasm may often obscure the acumen of the physician as well as the journalist."

It should be our aim to make pain of the parturient as easy as is feasible, constantly keeping in mind that the safety of the newborn and the mother is of greatest importance.

ANESTHESIA FOR ABDOMINAL SURGERY*

EDWARD B. TOLLY

The choice of an anesthetic agent or procedure for abdominal surgery is prefaced frequently by this question, "What do you use for operations on the gallbladder or what do you use for hysterectomy?" The same query might be applied to operations on the gastro-intestinal tract or on almost any portion of the body. The answer cannot be always direct and simple. Certain surgeons, because of previous experience, have definite preferences regarding the choice of anesthesia for abdominal surgery. Likewise, anesthesiologists have their preferences, likes and dislikes. Either one of these individuals may influence the other, and in some instances the patient offers a third opinion or request. This is particularly true in light of the popularity of pentothal sodium; many patients, because of hearsay or previous experience with anesthesia, request this agent.

I believe the solution to this problem of the choice of type of anesthesia for abdominal surgery lies in proper understanding of a given situation by the anesthesiologist, the surgeon and, whenever possible, the patient. Proficiency in the administration and use of anesthetic agents and procedures, like surgical dexterity and judgment, comes from experience, study and a consideration of previous errors. There is no substitute, to my knowledge, for an experienced surgical team and this means the surgeon, his assistants and the anesthesiologists. Most surgeons, I believe, would prefer to work each time with the same individuals, particularly with the same anesthesiologists, if possible. Efficient anesthesia is not so much a matter of the particular agent or method of anesthesia used, provided the surgeon

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knows the capabilities of the anesthesiologist and, I might add, provided the reverse situation be true also, as it is a matter of choosing the type of anesthesia which, under a certain set of circumstances, will be safest for the patient.

EVALUATION OF THE PATIENT

All of the medical data pertinent to the individual patient should be available and a discussion of the problem should be carried out by the surgeon and the anesthesiologist; then the patient should be informed that in the opinion of the surgeon and the anesthesiologist, such a type of anesthesia would be best for the operation required. This approach assures the patient that at least two individuals are interested vitally in a problem which has given them considerable concern; namely, "How do I go to sleep, or do I?"

AGENTS AND METHODS OF ANESTHESIA

It is quite natural that some form of general anesthesia is requested by most patients for abdominal surgery and unquestionably the greatest percentage of laparotomies are performed with the patient under general anesthesia, for which purpose ether is probably the main anesthetic agent. Nitrous oxide or, perhaps, ethylene is used as the induction agent. The almost universal safety of diethyl ether for children and adult persons makes it very popular. It is true that more nausea and vomiting attend its use than occurs with cyclopropane or the combination of solution of tribromethanol (avertin) (rectally) with cyclopropane. The contraindications to ether are actually very few and pulmonary tuberculosis (active) is probably the most definite. Cyclopropane, because it is pleasant to inhale, nonirritating and rapid in its action, is quite popular, particularly now that curare can be used as an aid in obtaining surgical relaxation without resorting to the controlled method of respiration. Certain cardiac irregularities do develop in certain individuals under cyclopropane anesthesia. These usually occur in the light planes of surgical anesthesia and are abolished when the depth of surgical anesthesia is increased. It is the consensus at the present time that if certain types of arrhythmia do occur the introduction of a little ether into the anesthetic mixture will usually abolish these cardiac irregularities. It is my opinion that prolonged administration of cyclopropane anesthesia for abdominal surgery or for thoracic surgery should be watched carefully because of the fact that the systolic blood pressure, which has a tendency to be reasonably well maintained during surgical anesthesia with this agent, tends to fall rather abruptly after administration of the anesthetic agent is terminated. Not infrequently the patients enter into a state of hypotension which may reach the level of surgical shock within a few moments. This phenomenon does not occur, as a rule, during the shorter administrations of cyclopropane, particularly when the depth of surgical anesthesia is kept in either plane 1 or 2. I think it is very well to emphasize this point that aberrations in blood pressure may follow the prolonged administration of cyclopropane and that precautions should be taken to prevent this drop in pressure. Intravenous administration of fluids should be started in sufficient time to prevent any marked deviation in blood pressure. Dextrose solutions, plasma or whole blood transfusions may be necessary. The advantage of using curare or

d-tubocurarine with cyclopropane anesthesia for abdominal surgery lies in the fact that this agent (curare) can be utilized to produce the muscular relaxation necessary to accomplish the surgical operation so that the depth of general anesthesia incident to the administration of cyclopropane can be kept at the level of plane 2 or slightly below.

The use of an intratracheal tube during the administration of any inhalation anesthetic agent has been established as a very excellent means of maintaining an adequate airway for the patient, serves to minimize the amount of anesthetic agent required and provides a means of artificial pulmonary ventilation should this procedure be required. Either the nasal or oral route of intubation may be used. I believe that an intratracheal tube should be used in the majority of cases in which cyclopropane and curare are used in combination inasmuch as momentary periods of apnea may occur in certain individuals. The use of an intratracheal tube is a definite safety precaution.

The amount of curare or d-tubocurarine which may be required in individual cases varies. Curare should be administered intravenously in fractional doses just prior to the opening of the peritoneum in cases of laparotomy. At the time of the administration of curare the flow of anesthetic gases or vapors should be momentarily turned off and basal oxygen administration maintained. The pharmacologic effect of curare on respiratory volume can be noted by watching the breathing bag on the gas machine. When the respiratory excursions become definitely shallow one usually will note concomitantly that the abdominal muscles are also relaxed. The effect of d-tubocurarine usually lasts for twenty-five to thirty minutes. Not infrequently when the operation has been completed and the peritoneum is to be closed, additional intravenous administration of this agent will be required. The same technic as that previously described should be used in this juncture. Again a word of caution is indicated concerning the use of curare to secure relaxation in closure of the abdomen. In certain individuals who have had curare for closure a transient depression of respiration occurs after the closure of the abdomen. This is probably due to the fact that sensory and motor stimuli are no longer present and respiration is not reflexly activated by these stimuli. It is important, therefore, to watch the patient closely when he is returned to his room to make sure that an adequate airway is maintained and that adequate pulmonary ventilation continues. This sequence of events may be noted with ether and curare, nitrous oxide and curare, pentothal sodium and curare, or with practically any combination of these agents. In the event of physiologic overdose from curare, the administration of neostigmine (pharmacologic antidote) combined with the administration of oxygen by means of artificial pulmonary ventilation is indicated.

CONTINUOUS SPINAL ANESTHESIA

The advantages of the method of continuous spinal anesthesia in which a ureteral catheter or the Lemmon malleable needle is used are (1) a relatively nontoxic agent may be administered intrathecally in divided doses as they are required, (2) this method prevents the tendency to administer the large initial doses which may be given when a single subarachnoid spinal injection

is used, and (3) it permits the surgeon to have practically unlimited operating time thereby preventing unnecessary haste. The continuous method of spinal anesthesia is recommended in those individuals who are suitable candidates for spinal anesthesia for the repair of ventral or inguinal hernia, for total cystectomy with transplantation of the ureters and for extensive operations on the gastro-intestinal and biliary tracts. The main disadvantage of any type of spinal anesthesia for operations in the upper part of the abdomen is the relatively high incidence of nausea or vomiting. This does not hold true for operations in the lower part of the abdomen, as a rule. In my experience I have found that the judicious intravenous use of pentothal sodium will control this problem of nausea or vomiting. Pentothal sodium should not be administered, however, until the full extent of the action of the spinal anesthetic agent has been determined. By this I mean the dermatome level to which the anesthetic agent has risen in the subarachnoid space. Obviously, as respirations become shallow as a result of paralysis of the intercostal muscles incident to spinal anesthesia, one should be very cautious in administering pentothal sodium at such a stage. The ureteral catheter technic has been mechanically more satisfactory, in my experience, than that of the malleable needle and it offers the additional advantages of allowing greater mobility of the patient, particularly for orthopedic operations, and of eliminating the requirement for a bulky mattress. Whereas various combinations of anesthetic agents, such as tetracaine (pontocaine) hydrochloride and dextrose or other solutions of anesthetic agents lighter or heavier than the spinal fluid, are used for abdominal operations, it is my impression that for operations which are reasonably extensive, the continuous method of spinal anesthesia is sounder physiologically.

I think a mistake is made not infrequently in the use of pentothal sodium as a supplement to the inadequate spinal anesthesia which may be obtained when the single dose method is used. The situation is usually one in which the spinal anesthetic agent does not give motor and sensory relaxation at levels sufficiently high anatomically to encompass the limits of the incision. When this situation arises one usually ends up by using a fairly large amount of pentothal sodium and, more likely than not, by switching to some combination of inhalation anesthetic agents in addition to the agents already administered. This is usually an unsatisfactory situation for the surgeon, as is well known, not to mention the fact that it is embarrassing for the anesthesiologist, because the respiratory depression which is usually present after inadequate spinal anesthesia plus use of pentothal sodium is sufficiently marked so that the introduction of an inhalation anesthetic agent is a slow and tedious process.

Regional block infiltration of the skin, subcutaneous tissue and fascia overlying the abdominal muscles is a method of anesthesia to be considered when surgical risk is great; the so-called abdominal wall block may be justifiably combined with light inhalation anesthesia or with the use of pentothal sodium or any one of several inhalation agents, with or without administration of curare. Certain surgeons have found that the use of regional block of the abdominal wall, plus infiltration of the parietal peritoneum and block of the anterior splanchnic nerves, has worked well for operations on the stomach and biliary tract. In certain individuals who are not of the

robust, athletic type, this method of anesthesia is satisfactory. I believe that the success of this method depends chiefly on the co-operation of the patient and the diligence, skill and patience of the surgeon. Regional block of the abdominal wall, plus block of the anterior splanchnic nerves, is not satisfactory for lower abdominal operations.

In bilateral intercostal nerve block by injection of the intercostal nerves in the anterior axillary line, the block usually includes the eleventh, tenth, ninth, eighth, seventh and sixth thoracic nerves. Five c.c. of 1 per cent solution of metycaïne hydrochloride with epinephrine is injected at each site. In individuals who are not of the robust type this regional anesthetic procedure gives reasonably satisfactory anesthesia for upper abdominal operations. It may be necessary to combine it with intravenous pentothal sodium anesthesia or with light gas-oxygen inhalation anesthesia.

SUPPORTIVE MEASURES IN ABDOMINAL SURGERY

The careful intravenous use of fluids, such as dextrose and saline solutions, and plasma and blood transfusions, needs little comment. Blood should be administered whenever the patient's condition seems to warrant it, and its use is contingent on the physical status of the patient prior to operation and on the amount of blood loss and surgical trauma during operation. Certain vasopressor agents, such as the soluble salts of ephedrine and neosynephrin, are of definite service to help maintain blood pressure and capillary tone when used either alone or in conjunction with the intravenous use of various types of fluids. They should not be relied on entirely to maintain adequate circulating blood volume.

The anesthesiologist can be of definite service to the surgeon, particularly in gastric surgery, by his ability to introduce various types of stomach tubes during surgical anesthesia. The advantage of having a rubber tube in situ at the time of operation is very vital to the postoperative convalescence following certain types of surgery. The ability to have these tubes accurately inserted while the patient is on the operating table rather than later when he is in his room, during the period of recovery, is of very definite value.

Among the endoscopic procedures which the anesthesiologist should be able to offer is that of suction bronchoscopy. Not infrequently large amounts of mucus accumulate in the tracheobronchial tree during the course of the operation and, unless the mucus is adequately aspirated, the incidence of pulmonary complications usually rises. Bronchoscopic aspiration is not recommended in every case, obviously, but should be resorted to when there is definitely an excessive amount of mucoid material present during the administration of the anesthetic agent. The optimal time for carrying out this procedure is at the termination of the operation before the patient has regained his throat reflexes, but aspiration may be resorted to at any time during the postoperative period should excessive accumulations of mucus occur with or without evidences of atelectasis. This type of care, I believe, will gradually fall more and more into the hands of the qualified anesthesiologist. Additional supportive therapy in the form of oxygen administration should be used whenever necessary.

SUMMARY

The choice of anesthesia for abdominal surgery cannot be stated didactically. Of more importance than the anesthetic agent or procedure are the skill and judgment of the anesthesiologist. Of practically equal importance is the teamwork between the surgeon and anesthesiologist which will serve to give the patient the safest anesthetic agent possible and in a sufficiently satisfactory manner so that the best surgical result can be accomplished.

General anesthesia has its own place as a choice of procedure in abdominal surgery. Likewise, regional anesthesia, including spinal, has its merits. Various agents, such as pentothal sodium, curare and cyclopropane, can be employed in combination with other anesthetic agents and procedures. Each case should be evaluated and where possible the anesthesia "tailor made" for the operation to be done, keeping in mind again the fact that the greatest safety to the patient is of first importance.

ANESTHETIC ACTION OF BETA-DIMETHYLAMINOETHYL
BENZHYDRYL ETHER HYDROCHLORIDE (BENADRYL) IN
THE SKIN OF HUMAN BEINGS*

MIL0 D. LEAVITT, Jr. AND CHARLES F. CODE

A study was made of the local anesthetic effect of beta-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl) when injected into the skin of human beings. The results were as follows: 1. By means of electric algometric determinations, benadryl in dilutions of 1:500, 1:1,000, 1:5,000, 1:10,000 and 1:20,000 was found to possess anesthetic potencies similar to those of procaine in dilutions of 1:200, 1:400, 1:800, 1:1,600 and 1:3,200 respectively. 2. Benadryl in concentrations greater than 1:500 (2 mg. per cubic centimeter) proved to be exceedingly irritating when injected into human skin, causing tissue necrosis and ulceration in four of ten subjects tested.

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MISCELLANEOUS

ANTIBIOTIC SUBSTANCES IN PEDIATRICS*

ROGER L. J. KENNEDY AND WALLACE E. HERRELL

The role of antibiotic agents in medicine and more particularly in pediatrics has come to be so great that a brief discussion of the subject must be categorical and only facts that permit of dogmatic presentation can be offered in the allotted time. The general subject of the role of antibiotic substances in therapy has been rather extensively reviewed elsewhere.

In general, antibiotic agents of microbial origin are derived from three general sources; namely, bacteria, molds or fungi and actinomycetes. Only the most important from the standpoint of therapy will be mentioned.

The most important antibiotic preparation derived from bacteria is gramicidin, now commonly known as "tyrothricin." This substance is elaborated by a soil bacillus and exerts a marked antibacterial effect on certain gram-positive pathogens. Because of its marked hemolytic property, it is of only limited value in the treatment of infections. It can be used satisfactorily as a local application but because of its toxic effect it cannot be administered under conditions in which it will come in direct contact with the blood stream. If tyrothricin is to be used locally, the usual procedure is to prepare a solution which contains 500 to 1,000 micrograms of the substance in each cubic centimeter of physiologic saline solution.

Penicillin is an example of an antibiotic agent derived from molds. It is well known that this substance was first described by Fleming and was derived from the mold, *Penicillium notatum*. To date, it has proved to be the most important antibiotic agent available.

The most recent antibiotic substance which possesses important therapeutic possibilities is streptomycin. This antibiotic agent, described by Schatz, Bugie and Waksman, is an example of one derived from actinomycetes. The source of this substance is *Actinomyces griseus*.

All of these substances exhibit a selective antibacterial action. Gramicidin and penicillin inhibit the growth of gram-positive organisms; penicillin also inhibits the growth of certain important gram-negative microbes, such as *Neisseria intracellularis* and *Neisseria gonorrhoeae*. Streptomycin, on the other hand, inhibits the growth of several important gram-negative microbes and also appears to inhibit the growth of *Mycobacterium tuberculosis*. Penicillin now appears to be a substance that is composed of several different fractions which have been designated K, G and X. It is important to remember that some fractions are relatively inactive in the body and, therefore, it is essential that something be known concerning the content of a given preparation of penicillin. For example, penicillin which is high in the K fraction is likely to yield poor therapeutic results. It is obviously im-

* From the Wisconsin Medical Journal, 46:502-515 (May) 1947.

portant, therefore, that preparations which are offered for therapeutic use must contain a preponderance of the therapeutically effective fractions such as G and X.

The present discussion will deal primarily with the antibacterial activity and the clinical use of penicillin and streptomycin.

ANTIBACTERIAL ACTIVITY OF PENICILLIN AND STREPTOMYCIN

Certain pathogenic organisms are inhibited to varying degrees by both penicillin and streptomycin but at times there is marked difference in sensitivity of various strains of the same organism to these agents. This is especially true in respect to streptomycin. For example, although certain strains of *Escherichia coli* are sensitive to streptomycin, other strains may be extremely resistant. The occurrence of variation among strains must be borne in mind in connection with the treatment of infections and this fact immediately suggests the importance of testing various organisms for sensitivity before and during treatment.

PHARMACOLOGIC ASPECTS OF PENICILLIN AND STREPTOMYCIN

The absorption of penicillin after subcutaneous administration is more variable than is that of streptomycin. After intramuscular or intravenous administration of a single dose of penicillin the concentration in the blood usually reaches a peak within an hour or two and at the end of three or four hours little of the drug can be demonstrated in the blood. The concentration of streptomycin in the blood after an injection by the intravenous, intramuscular or even subcutaneous method usually remains sufficiently high to be demonstrable for several hours. Penicillin does not appear to accumulate in the body after repeated injections whereas the opposite appears to be true in respect to streptomycin.

Both penicillin and streptomycin diffuse fairly well throughout the tissues of the body. Although only small amounts of penicillin ordinarily diffuse through the intact meninges, in the presence of inflammation amounts which are antibacterial find their way into the cerebrospinal fluid. It also penetrates into ocular tissue and into lacrimal, salivary, pancreatic and peritoneal secretions. Penicillin has been found in synovial fluids in concentrations of approximately a half of that found in the blood. It also diffuses into the placenta and thence into the fetal circulation in amounts sufficient to be effective for treatment of infections of the fetus within the uterus.

Streptomycin, too, diffuses readily into the various tissues and fluids of the body, including the meninges, placenta, peritoneal fluid, pleural fluid and vitreous humor.

Both drugs are excreted in the urine. From 60 to 80 per cent of the amount of either antibiotic substance injected may be recovered in the urine within twenty-four hours after injection. Both are also concentrated and excreted in the bile.

DOSAGE AND METHODS OF ADMINISTRATION

Penicillin.—The proper dose of penicillin for infants and children varies from 40,000 to 200,000 units per twenty-four hours depending on the age of the patient and the severity of the infection, except that larger doses are

required for treatment of patients with bacteriemia, including subacute bacterial endocarditis, and for patients suffering from actinomycosis.

Administration of penicillin by repeated intramuscular injections is the method of choice for infants and younger children, whereas either this method or that of continuous intravenous drip may be used for older children. In the intermittent intramuscular method, the dose for infants and young children is 5,000 to 10,000 Oxford units in 1 or 2 c.c. of physiologic saline solution every three hours. For older children the dose is similar to that for adults; namely, 20,000 to 30,000 Oxford units every three hours. The sites of administration most frequently employed are the outer upper quadrants of the buttocks and the deltoid regions. The sites of injection should be rotated from side to side.

Intramuscular administration of penicillin in a mixture of peanut oil and beeswax, which contains 300,000 units of penicillin (calcium) in 1 c.c., affords antibacterial concentrations of penicillin which frequently can be demonstrated as long as twenty-four hours after injection. This preparation is known as the "Romansky formula." It is particularly useful in the home in the treatment of patients who cannot be seen by the physician oftener than once in twenty-four hours. It can be administered into the muscles of the buttocks daily for several days without inconvenience or serious untoward reactions. Localized redness, which is due to an allergic reaction to the preparation and not to true inflammation, may develop at the site of injection. This reaction usually subsides when administration of the material is discontinued. Administration of antihistamine preparations, such as benadryl and pyribenzamine, likewise have been found effective in controlling this reaction.

Administration of penicillin by continuous intramuscular drip is not advocated.

The method of choice in the treatment of severe infections, such as bacteriemia, is that of intravenous drip. It can be employed in older children but its use in infants and younger children is attended by the usual difficulties involved in maintenance of any intravenous procedure. From 100,000 to 200,000 units of penicillin in 1 or 2 liters of physiologic saline solution can be made from stock solutions which contain 10,000 units of penicillin per cubic centimeter. The rate of flow should be about 20 to 25 drops per minute. The use of the veins on the dorsum of the hand allows the arm and hand to remain in a much more comfortable position than if an antecubital vein is employed.

Penicillin may be injected into various body cavities. For use in the pleural cavity, at least 50,000 units may be dissolved in 40 to 50 c.c. of physiologic saline solution. This amount may be injected into the pleural space daily. For introduction into the joint cavities or into the cerebrospinal canal, 10,000 units in 5 or 10 c.c. of physiologic saline solution is satisfactory.

The oral administration of penicillin is not advocated for the treatment of severe infections because the absorption, when given by this route, is variable in different individuals. For mild infections the drug may be given by mouth. However, oral use involves large doses. When given in tablet form, the minimal dose should be 50,000 units. In some cases this may have to be increased to 100,000 units. This dose should be given one and a

half hours before meals and one and a half hours after meals; the dose should be repeated once in the evening and once during the night. Another objection to this method of treatment is that of the expense involved.

Penicillin administered by nebulization has proved effective in several forms of pulmonary disease. For infants we have used a small tent into which penicillin has been introduced by means of oxygen and a glass nebulizer. The solution contains from 1,700 to 2,500 Oxford units per cubic centimeter. For older children a standard glass nebulizer is used and the patient is allowed to inhale 1 c.c. (5,000 units per cubic centimeter) of nebulized solution in ten minutes. This procedure is repeated at intervals of twenty to thirty minutes throughout the day.

Streptomycin.—The unit of dosage for streptomycin which has been recently adopted is based on the metric system: 1 gm. of streptomycin is equivalent to 1,000,000 original S units of Waksman.

Intermittent intramuscular injection is the method of choice for administration of streptomycin. Solutions which contain 100 to 250 mg. (100,000 to 250,000 S units) per cubic centimeter are most commonly used. Although streptomycin may be given intravenously, this procedure at times may result in local venous irritation. If the preparation is to be used intravenously, the daily dose should be dissolved in 1 or 2 liters of isotonic saline solution or in 5 per cent solution of glucose. One hundred milligrams of heparin may be added to each liter of solution in an effort to decrease the possibility of venous thrombosis.

When streptomycin is administered by intermittent intramuscular injection, the minimal daily dose appears to be 1 to 2 gm. (1,000,000 to 2,000,000 S units). This amount is divided into six or eight doses and administered at intervals of three to four hours. It has become rather standard practice at the Mayo Clinic to inject every four hours 2 or 3 c.c. of a solution which contains 100 mg. per cubic centimeter; thus, the total dose amounts to 1.2 to 1.8 gm. per twenty-four hours.

For use by the intrathecal route, 100 mg. of streptomycin dissolved in 5 or 10 c.c. of physiologic saline solution may be given every twenty-four or forty-eight hours.

Streptomycin can also be given by means of nebulization. Fifty milligrams of streptomycin in a cubic centimeter of solution can be inhaled and similar amounts can be inhaled at intervals throughout the day so that as much as 0.5 gm. (500,000 S units) per day may be administered in this manner.

Since streptomycin is not absorbed from the gastro-intestinal tract, its use by mouth should be limited to the treatment of patients with conditions in which reduction of the number of susceptible organisms in the intestine is desired. The dose for oral administration is 0.25 to 0.5 gm. (250,000 to 500,000 S units) given four times during each twenty-four hours. Whether or not streptomycin is superior to sulfonamides for the purpose of reducing organisms in the intestinal flora cannot be stated at this time.

CLINICAL USES OF PENICILLIN

Bacteriemia.—Penicillin is effective in treatment of bacteriemia due to *Staphylococcus aureus*, *Staphylococcus albus*, *Streptococcus pyogenes* (hemolytic streptococci), nonhemolytic streptococci or anaerobic strepto-

cocci (micro-aerophilic streptococci). Bacteriemia owing to *Diplococcus pneumoniae* and *Neisseria intracellularis* has been treated successfully with penicillin, but for patients who are severely ill the treatment with penicillin should be supplemented by administration of sulfadiazine. The concentration of sulfonamide in the blood should be maintained at 10 to 15 mg. per 100 c c.

Bacteriemia due to gram-negative organisms of the colon-typhoid-dysentery group and to organisms of the genus *Proteus*, *Pseudomonas aeruginosa* or *Klebsiella pneumoniae* (Friedländer's bacillus) and infections which involve the blood stream or heart, such as tularemia, brucellosis and malaria, will not respond to treatment with penicillin.

Subacute Bacterial Endocarditis.—Penicillin is of value in the treatment of patients suffering from subacute bacterial endocarditis which is due to strains of streptococci that are sensitive to the substance. The sensitivity of the organism involved should be determined before treatment is instituted. If the organism is sensitive to penicillin in concentrations of 0.01 to 0.1 unit per cubic centimeter, satisfactory results may be anticipated. The treatment should be continued four to six weeks. Although use of intravenous drip is the method of choice, satisfactory results can be obtained by the use of the method of repeated intramuscular administration. The minimal daily dose for infants and young children with this disease is 500,000 units. Older children require at least 1,000,000 units. There is some evidence that doses considerably greater than these produce more satisfactory results. However, it would appear that the most important consideration is the question of how long the patient is treated rather than how much penicillin is administered each day, provided that as much as 500,000 to 1,000,000 units is used.

Pericarditis and Rheumatic Fever.—Instillation of penicillin into the pericardial sac of patients with suppurative pericarditis may be of great value. Instillation may be carried out once every twenty-four to forty-eight hours.

Penicillin is of no value in the treatment of rheumatic fever.

Meningitis, Wounds of the Brain and Brain Abscess.—Meningitis due to *Neisseria intracellularis*, *Diplococcus pneumoniae*, *Staphylococcus pyogenes* and *Streptococcus pyogenes*, anaerobic streptococci and certain strains of green-producing streptococci may be treated successfully with penicillin. The drug should be given parenterally together with a few intrathecal instillations. Patients with meningitis due to *Neisseria intracellularis* and *Diplococcus pneumoniae* should receive sulfadiazine or sulfamerazine in addition to penicillin. For treatment of patients who are sensitive to either sulfonamides or penicillin, the other may be used alone with reasonable expectation of success.

Penicillin also has a prominent place in the treatment of wounds of the brain and brain abscess in which the infecting organism is sensitive to the drug. It can be applied locally together with sulfanilamide in the form of a powder which contains 5,000 Oxford units of penicillin to each gram of sulfanilamide. Solutions which contain 5,000 Oxford units of penicillin per cubic centimeter may be used for local instillation.

Penicillin is of little or no value in the treatment of infections of the central nervous system due to *Mycobacterium tuberculosis*, *Torula*, blastomycetes and *Hemophilus influenzae*.

Infections of the Eye.—Streptococcic, staphylococcic, pneumococcic, gonococcic, meningococcic and syphilitic infections of the eye respond to treatment with penicillin. Acute and chronic blepharitis, ophthalmitis, cellulitis and panophthalmitis have responded satisfactorily. Treatment of these conditions with penicillin should be by means of both local and systemic administration. Solutions or creams containing penicillin may be instilled into the eye every two or three hours. The solution usually employed contains 1,000 to 5,000 Oxford units of penicillin in each cubic centimeter of physiologic saline solution. Creams which contain from 250 to 1,000 Oxford units of penicillin per gram may be used in the treatment of superficial ulcerations and conjunctivitis. It has been recommended that penicillin should be used as a specific prophylactic agent in the Credé method of prevention of ophthalmia neonatorum; for this purpose four drops of a solution which contains 250 units of penicillin per cubic centimeter should be instilled into each eye every four hours for at least twenty-four to forty-eight hours.

Infections of the Paranasal Sinuses and Middle Ear.—Acute and subacute suppurative processes which involve the paranasal sinuses and middle ear respond to administration of penicillin in cases in which the organism present is sensitive to the action of the drug. Since the organisms usually found in these conditions are streptococci, staphylococci, pneumococci and micro-aerophilic streptococci, all of which are sensitive to penicillin, successful results can be anticipated. Patients whose infections of the sinuses and middle ear are in the early stages frequently can be cured without resort to surgical treatment. In chronic conditions, adequate surgical drainage and removal of foci may be necessary.

Acute Tonsillitis and Septic Sore Throat.—Penicillin is of value in the treatment of patients suffering from acute tonsillitis and septic sore throat due to *Streptococcus pyogenes*. It hardly seems necessary to use penicillin in the treatment of all patients who have tonsillitis. Probably the greatest value of penicillin is in the treatment of those patients who are intolerant to sulfonamides. Penicillin is also effective in the treatment of carriers of streptococci in the throat. It is of little or no value in the treatment of diphtheria.

Pneumonia.—Although penicillin is effective in the treatment of pneumococcal, staphylococcal or streptococcal pneumonia, it need not replace the use of sulfonamides unless the pneumonia is caused by organisms which are, or have become, resistant to sulfonamide compounds. There is some difference of opinion regarding the value of penicillin in the treatment of pneumonia of virus origin (primary atypical pneumonia). There is sufficient evidence to indicate that it is of value in treatment of ornithosis and psittacosis.

Bronchitis and Bronchiectasis.—There is also evidence to support the view that penicillin is of value in the treatment of bronchitis and bronchiectasis; this evidence was secured in cases in which penicillin was administered parenterally by nebulization. Preoperative treatment of patients with suppurative pulmonary disease reduces the amount of infection and the possibility of serious postoperative complications, such as empyema and generalized sepsis.

Infections of the respiratory tract in which penicillin is of no value are

cocci (micro-aerophilic streptococci). Bacteriemia owing to *Diplococcus pneumoniae* and *Neisseria intracellularis* has been treated successfully with penicillin, but for patients who are severely ill the treatment with penicillin should be supplemented by administration of sulfadiazine. The concentration of sulfonamide in the blood should be maintained at 10 to 15 mg. per 100 c.c.

Bacteriemia due to gram-negative organisms of the colon-typhoid-dysentery group and to organisms of the genus *Proteus*, *Pseudomonas aeruginosa* or *Klebsiella pneumoniae* (Friedländer's bacillus) and infections which involve the blood stream or heart, such as tularemia, brucellosis and malaria, will not respond to treatment with penicillin.

Subacute Bacterial Endocarditis.—Penicillin is of value in the treatment of patients suffering from subacute bacterial endocarditis which is due to strains of streptococci that are sensitive to the substance. The sensitivity of the organism involved should be determined before treatment is instituted. If the organism is sensitive to penicillin in concentrations of 0.01 to 0.1 unit per cubic centimeter, satisfactory results may be anticipated. The treatment should be continued four to six weeks. Although use of intravenous drip is the method of choice, satisfactory results can be obtained by the use of the method of repeated intramuscular administration. The minimal daily dose for infants and young children with this disease is 500,000 units. Older children require at least 1,000,000 units. There is some evidence that doses considerably greater than these produce more satisfactory results. However, it would appear that the most important consideration is the question of how long the patient is treated rather than how much penicillin is administered each day, provided that as much as 500,000 to 1,000,000 units is used.

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Infections of the respiratory tract in which penicillin is of no value are

tuberculosis, Friedländer pneumonia, fungus infections, blastomycosis, coccidioid granuloma and moniliasis.

Diseases of the Bones and Joints.—Penicillin is valuable in the treatment of acute osteomyelitis even in cases in which bacteriemia is present. Improvement should be evident within a day or two after commencement of treatment with penicillin. For children the dose is 100,000 to 200,000 units per day. Penicillin combined with surgical eradication of infectious foci and sequestra is helpful in the treatment of chronic osteomyelitis. In addition to its effects on the local lesion, its use tends to prevent complicating cellulitis and bacteriemia.

Treatment of osteomyelitis of the cranial and facial bones and of acute, subacute and chronic mastoiditis with penicillin has an established place. Pyogenic arthritis of streptococcal, staphylococcal, pneumococcal or gonococcal origin should be treated by administration of penicillin both systemically and by instillation directly into the affected joint at intervals of forty-eight hours.

Chronic rheumatoid arthritis, intermittent hydrops and tuberculosis of the bones and joints, as well as arthritis due to brucellosis and typhoid fever, will not respond to treatment with penicillin.

Infections of the Skin and Soft Tissue.—Penicillin is useful in the treatment of secondarily infected eczema, particularly when the infecting organism is *Streptococcus pyogenes* or *Staphylococcus aureus*. In such cases it should be administered by the parenteral route together with local application of a cream containing approximately 1,000 Oxford units of penicillin per gram. Furunculosis and carbuncles also respond favorably to the parenteral administration of the drug.

Impetigo occurring in the newly born in nurseries as well as in children of all ages responds to as little as two intramuscular injections of 5,000 Oxford units of penicillin each. The local application of penicillin ointment (1,000 units per gram) is effective and is without the danger of reactions such as may occur after the use of sulfathiazole or other sulfonamides.

Cellulitis, such as that involving the floor of the mouth (Ludwig's angina), frequently may be treated satisfactorily with penicillin alone. Thrombosis of the cavernous or lateral sinuses has also responded to intensive parenteral administration of penicillin. Acute mastitis in infants has been treated effectively. Postoperative parotitis also responds.

Infected burns may be kept free from susceptible organisms and skin grafting may be facilitated by the use of penicillin.

In cases of smallpox secondary infection by *Staphylococcus aureus* and the resultant toxemia and bacteriemia may be controlled by administration of penicillin. Conditions of the skin that do not respond to administration of penicillin are chickenpox, herpes, acne, pemphigus, lupus erythematosus, blastomycosis, coccidioidomycosis, yeast infections and sporotrichosis. Other infections that do not respond are histoplasmosis, epidemic parotitis, myositis and dermatomyositis. Penicillin has not proved of value in the treatment of tularemia.

Infections of the Genito-urinary Tract.—Perinephritic abscess and carbuncles of the kidney may be successfully treated with penicillin without resort to surgical drainage. In some cases combined use of penicillin and surgical treatment has been found necessary. Most instances of pyelo-

nephritis, pyelitis and cystitis are due to relatively insensitive gram-negative organisms. If the infecting organism is sensitive to penicillin, satisfactory results of treatment can be expected, provided that obstruction in the urinary tract is not present. If gram-negative organisms are present, treatment with sulfathiazole will be found most effective. Gonorrhea, whether of the urinary tract or of other organs or systems, responds almost universally to treatment with penicillin.

Syphilis.—A sufficient number of reports on the successful use of penicillin in the treatment of congenital syphilis are available to indicate that it is of established value in the treatment of this condition.

Gas Gangrene.—The organisms commonly associated with gas gangrene have been proved to be sensitive to the action of penicillin. Since, however, the drug does not neutralize the toxins present in this condition, its use should be combined with full therapeutic doses of polyvalent gas gangrene antitoxin.

Actinomycosis.—In agreement with the fact that nearly all strains of *Actinomyces bovis* are sensitive to the action of penicillin, treatment of the maxillofacial and thoracic-abdominal forms of actinomycosis with penicillin has been found effective. Surgical drainage may be needed also. Rather large doses, that is, 250,000 units of penicillin for infants, 500,000 units for young children and as much as 1,000,000 units for older children, should be used each day for at least thirty days.

Rat-bite Fever.—Rat-bite fever due to infection by either *Spirillum minus* or *Streptobacillus moniliformis* has been treated effectively with penicillin. Recovery after its use has been prompt.

Infections Due to *Borrelia Vincenti* (Vincent's Spirillum).—Necrotic lesions of the mouth (Vincent's angina) often heal within twenty-four to forty-eight hours after treatment with penicillin is begun. The drug is usually administered parenterally, although in older children it may be applied locally in the form of a solution containing 1,000 Oxford units per cubic centimeter or by means of troches containing 5,000 Oxford units which are held in the mouth until dissolved.

Tetanus.—*Clostridium tetani* is sensitive to the action of penicillin. It should be emphasized, however, that treatment of tetanus with penicillin alone should not be considered enough; the neutralizing effect of antitoxin is also essential.

Peritonitis.—Penicillin may be of some value in the treatment of peritonitis but its use should be combined with intraperitoneal administration of sulfonamides.

Agranulocytosis.—Penicillin is the treatment of choice in cases of agranulocytosis.

CLINICAL USES AND LIMITATIONS OF STREPTOMYCIN

Streptomycin has been introduced too recently to permit final statements to be made concerning its clinical effectiveness.

Tuberculosis.—There seems little doubt, in view of the results reported by Feldman and Hirschaw and Feldman, Hirschaw and Mann, that streptomycin exerts a marked suppressive, as well as curative, effect on the course of experimental tuberculosis in guinea pigs. To establish its value in the treatment of clinical tuberculosis will require a long period of clinical trials.

and observation. Its use in children has been limited to cases of tuberculous meningitis, tuberculosis of the hilar lymph nodes and primary tuberculous infection of the lungs. The results to date are inconclusive. Of four children who were given streptomycin for tuberculous meningitis, two died within a short period; one lived for three months but the clinical condition was not good at any time and one child who was treated for six months is now clinically well so far as tuberculosis is concerned. However, there appears to be complete deafness and the child exhibits a definite personality change. The patients who were suffering from primary tuberculosis and tuberculosis of the hilar lymph nodes are still under observation.

Infections of the Urinary Tract.—While streptomycin has proved to be helpful in treatment of infections of the urinary tract due to *Escherichia coli* and *Pseudomonas aeruginosa*, its chief value appears to be in cases of infection by *Proteus ammoniae* and *Aerobacter aerogenes*. Since some strains of these organisms may rapidly develop resistance to streptomycin, treatment should involve administration of large doses (1 to 2 gm.) daily for a short time (five or six days). It is known that streptomycin produces its maximal bacterial inhibition in alkaline mediums. For this reason it may be desirable, whenever possible, to render the urine alkaline. Likewise, foreign bodies and obstruction should be removed from the urinary tract before administration of streptomycin is begun.

Bacteriemia.—Reports are now on record indicating that streptomycin is of value in the treatment of bacteriemia owing to *Escherichia coli*, *Aerobacter aerogenes*, *salmonellae* and *Proteus ammoniae*. Whenever such infections are to be treated in children, streptomycin should be administered by intravenous drip, if feasible, and 1 to 2 gm. of the drug given each day for at least the first few days.

Tularemia.—At present streptomycin appears to be the drug of choice in the treatment of tularemia.

Undulant Fever.—Results of experience to date indicate that streptomycin has only a suppressive effect in the treatment of undulant fever in the acute or early stages. It is of doubtful or no value in the treatment of chronic brucellosis.

Miscellaneous Infections.—The effectiveness of streptomycin in the treatment of infections due to *Klebsiella pneumoniae* (Friedländer's bacillus), *Eberthella typhosa* and *Hemophilus pertussis* requires further investigation before final statements can be made. Results of the use of streptomycin in the treatment of syphilis have been questionable to date.

Alexander and her colleagues have reported the successful use of streptomycin in the treatment of meningitis due to *Hemophilus influenzae*. In children who have been treated at the Mayo Clinic, the results have been satisfactory and it is likely that the drug will prove to be a valuable adjunct in the treatment of this disease. In severe infections it is recommended that administration of streptomycin be combined with that of sulfonamides; in some instances, administration of sulfonamides and streptomycin in combination with serum may be necessary.

TOXICITY OF PENICILLIN AND STREPTOMYCIN

Penicillin.—Penicillin exerts few undesirable effects. Pain at the site of intramuscular injection, venous irritation at the site of injection and con-

tinuous toxic manifestations are the major inconveniences associated with its administration. The pain at the site of intramuscular injection may be reduced by application of an ice bag for a few minutes before injection is made or by inclusion of 1 c.c. of 2 per cent solution of procaine in each 15 c.c. of the stock solution (10,000 units of penicillin per cubic centimeter) which is injected. The addition of 100 mg. of heparin to each liter of the solution of penicillin which is to be administered by intravenous drip will tend to overcome local venous irritation.

Urticaria, irritative dermatitis and pruritus may follow the administration of penicillin. Under such circumstances, if the infection for which treatment is being given does not endanger life, the use of the drug may be discontinued. Urticaria and pruritus usually respond to the oral administration of benadryl in doses ranging from 10 mg. in an elixir to 50 mg. in a capsule three or four times a day.

Streptomycin.—The toxic effects of streptomycin are similar to those of penicillin and the method of handling such undesirable reactions are the same. However, prolonged treatment with streptomycin may be followed by vertigo, ataxia and nerve deafness. Whether these are due to streptomycin or to impurities in the preparation has not been determined with certainty. If any of these reactions develop, another preparation of the drug may be tried or the use of the drug may be discontinued

STREPTOMYCIN*

WALLACE E. HERRELL

The great interest in streptomycin lies in the fact that it is effective against certain important gram-negative organisms, many of which are not inhibited by penicillin. Furthermore, streptomycin appears to exert an antibacterial effect on *Mycobacterium tuberculosis*. At the Mayo Clinic studies on streptomycin began in the spring of 1944. Feldman and Hinshaw later reported on the possible effect of streptomycin in experimental and clinical tuberculosis. My interest in streptomycin has been in its use in the treatment of infections other than tuberculosis, particularly those due to sensitive gram-negative organisms.

CLINICAL RESULTS

Some of the most striking clinical results obtained to date with streptomycin have been those which followed its use in the treatment of tularemia. In this disease streptomycin has clearly established its value. In the past, patients who had tularemia were frequently ill for as long as twelve to sixteen weeks and many failed to survive. To date no failures have been reported in cases of tularemia treated with streptomycin. The average dose of streptomycin used has been 2 gm. per day for seven to ten days. The

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clinical improvement is dramatic and recovery has been uneventful in all forms of tularemia treated.

Bacteriemia and infections of the urinary tract due to *Escherichia coli* also have responded satisfactorily to streptomycin. There have been some failures in this group due to the fact that the organism was resistant or became resistant to streptomycin.

Rather satisfactory results have been obtained in cases of bacteriemia and infections of the urinary tract owing to *Proteus ammoniae* and *Aerobacter aerogenes*. Infections of the urinary tract should be treated intensively for a short period, that is, five to seven days. Treatment should not be begun until foreign bodies and obstruction have been removed from the urinary tract. The presence of foreign bodies or obstruction favors the development of resistance to streptomycin.

The organism, *Hemophilus influenzae*, is sensitive to the action of streptomycin. It is not surprising, therefore, that satisfactory results have been obtained in the treatment of influenza meningitis with streptomycin. It is generally agreed, however, that in the severe cases treatment with streptomycin should be combined with sulfonamide therapy and probably also combined with serum therapy. Likewise, *Hemophilus pertussis* is sensitive to the action of streptomycin but clinical results to date have not progressed sufficiently so that any definite statements can be made about its value in whooping cough. Clinical trials are under way.

Use of this antibiotic has been found of value in the treatment of Friedländer pneumonia and it also appears helpful in the treatment of ozena. Unfortunately, the incidence of recurrence and the incidence of the development of resistance on the part of the organism is rather prominent in this group of infections.

In spite of the fact that the organisms belonging to the typhoid or paratyphoid group are reasonably sensitive to streptomycin in the test tube, the clinical results of its use to date in the treatment of typhoid fever have not been encouraging.

Although streptomycin for the most part is effective against gram-negative organisms, a few strains of *Staphylococcus aureus*, a gram-positive organism, also are sensitive to streptomycin. My colleagues and I have had occasion to see recoveries from staphylococcal bacteriemia when the organisms were resistant to penicillin but yielded to streptomycin.

The organism responsible for undulant fever is moderately sensitive to this antibiotic. Unfortunately, streptomycin was hailed as a cure for this rather common infection and this is not the case. Experience to date would lead me to conclude that streptomycin may be of some value in the treatment of undulant fever in the early acute stage with or without positive blood cultures. I do not believe, however, that this beneficial effect is much greater than that which can be obtained by using three ten day courses of treatment with one of the sulfonamides, such as sulfadiazine. It should be pointed out also that the results obtained in the early acute stages can be evaluated only with difficulty for many persons recover spontaneously and blood cultures become negative for the organisms even without treatment. In the treatment of so-called chronic undulant fever or brucellosis of months' or years' standing, I am convinced that streptomycin is of little or no value.

I am not qualified to speak with authority on the chemotherapy of tuberculosis. I believe that Feldman and Hinshaw, as well as other investigators, are of the opinion that streptomycin exerts a suppressive effect but has not been hailed as a cure. As the matter stands, it is an important addition to standard forms of treatment. Unjustified publicity can lead to only one result. Patients will clamor for this new form of treatment and if its value is overstressed, patients may refuse conventional forms of treatment including sanatorial care. It is the responsibility of the medical profession to see that this does not occur.

TOXIC REACTIONS

Certain toxic cutaneous reactions are not unlike those that follow the administration of penicillin to certain sensitive individuals. The reaction may take the form of a maculopapular rash or generalized urticaria. If use of the drug is discontinued, the cutaneous reaction will usually subside. On occasion my colleagues and I have been able to continue administration of streptomycin after a cutaneous reaction has occurred by changing from one batch of streptomycin to another. In the management of the cutaneous reactions benadryl (β -dimethylaminoethyl benzhydryl ether hydrochloride) or pyribenzamine (N' -pyridyl- N' -benzyl- N -dimethylethylene diamine hydrochloride) is rather helpful. The usual dose of benadryl or pyribenzamine is 50 mg. three times per day. Individuals who are sensitive and who handle the solutions of streptomycin in the laboratory or elsewhere may develop a real dermatitis.

Perhaps the most important toxic reaction encountered in connection with the use of streptomycin is the neurotoxic effect on the eighth nerve. This reaction imposes a real problem but it is not insurmountable. As a rule it is not encountered when streptomycin is used for a short period as for acute infections although on occasion I have seen it develop soon after treatment is started. It is encountered rather frequently, however, when streptomycin is used for long periods as is necessary in the treatment of tuberculosis. The reaction may take the form of vertigo which results from damage to the vestibular branch or the reaction may take the form of a nerve deafness which results from damage to the auditory branch of the eighth nerve. Both reactions may occur in the same patient. Experience shows, however, that the reaction of the eighth nerve usually will subside if administration of the streptomycin is discontinued soon after symptoms appear. This is a rather selective neurotoxic effect.

DEVELOPMENT OF RESISTANCE

Certain organisms at times will develop resistance to streptomycin; in fact, some organisms will develop resistance to streptomycin with incredible rapidity. In the treatment of acute infections, therefore, intensive treatment for a short period of time is exceedingly important. Every effort should be made to reduce factors which favor resistance. Walled-off abscesses when present should be drained. Foreign bodies should be removed. Stasis and obstruction such as occur in infections of the urinary tract should be dealt with before treatment with streptomycin is begun. Finally, the pathogenic organisms should be tested for sensitivity before and during treatment. This testing necessitates frequent recourse to laboratory pro-

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cedures which only the bacteriologist can furnish. If an organism is resistant, or becomes resistant, to streptomycin, treatment will necessarily fail. The development of resistance on the part of the organism is far more important in connection with streptomycin therapy than experience at the clinic has shown it to be with penicillin.

STREPTOMYCIN IN TUBERCULOSIS*

H. CORWIN HINSHAW, MARJORIE M. PYLE AND WILLIAM H. FELDMAN

Although attempts to attack tuberculosis by chemotherapeutic means are as old as our knowledge of the disease, it was not until 1940 that a substance was found capable of arresting tuberculosis in vivo. In that year Feldman, Hinshaw and Moses reported that promin (sodium p, p'-diaminodiphenylsulfone-N, N'-dextrose sulfonate) had a striking effect on tuberculosis induced in guinea pigs. A few other drugs of the sulfone series were found to have a similar suppressive effect on experimental tuberculosis, and attempts to use these drugs clinically followed. The results were suggestive but never fully convincing, possibly because the sulfone compounds were found to be too toxic to permit adequate treatment of tuberculosis of human beings.

From the first, streptomycin gave great promise as an agent capable of suppressing tuberculosis. In their early reports Schatz and Waksman noted that a human strain of *Mycobacterium tuberculosis* was sensitive to streptomycin in vitro. Investigations of this antibiotic agent were begun in April, 1944, at the Mayo Foundation with the methods previously developed for chemotherapeutic testing in experimental tuberculosis. These investigations proved conclusively that streptomycin consistently would arrest and at times even apparently eradicate well-established tuberculosis in the highly susceptible guinea pig.

In the most severely controlled of the experiments, forty-nine guinea pigs were infected with a virulent standard human strain of tubercle bacilli. Forty-two days later results of tuberculin tests of all the animals were positive. On the forty-eighth day of infection biopsy of the liver was performed in each case and histologic evidence of the disease was obtained. On the forty-ninth day after infection twenty-five of the animals were treated with streptomycin. Treatment was continued for a total of 166 days. Approximately 70 per cent of the control animals succumbed to infection within this period, whereas only 8 per cent of the animals treated died before the experiment was terminated 215 days after infection.

At necropsy all control animals showed evidence of severe, widely disseminated tuberculosis. In marked contrast, the treated animals showed little or no gross or microscopic evidence of infection. In a majority of animals treatment with streptomycin must have had a suppressive rather than a sterilizing effect on the infection, because tubercle bacilli were re-

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covered by animal inoculation tests from the spleens of fifteen of the twenty-five treated animals. However, in nine of the treated animals the sensitivity to tuberculin was reversed from positive to negative, and in only two of this group were tubercle bacilli recovered from the spleens by animal inoculation. Streptomycin was tolerated well by the test animals, and there was no histologic evidence of drug toxicity in any of the organs. Youmans and McCarter reported equally encouraging results from the treatment with streptomycin of mice infected experimentally with tuberculosis.

CLINICAL USE OF STREPTOMYCIN*

The clinical use of streptomycin for tuberculosis was begun in December, 1944. In the last two years streptomycin has been used by our colleagues and us in more than 100 cases of tuberculosis of various types. A preliminary report of the earlier work was given in September, 1945, and more recently a more comprehensive account was published in collaboration with Dr. Karl H. Pfuetze. At present approximately 200 additional patients are being treated with streptomycin at selected institutions, under the auspices of the American Trudeau Society. In addition, a large number of patients are receiving streptomycin for tuberculosis in other institutions. When the mass of data from all this investigation is assembled, perhaps within a few months, it should be possible to make a more accurate appraisal of the drug, not only in regard to its therapeutic efficacy in tuberculosis, but also as to its toxicity and such factors as the effective dosage and optimal duration of treatment.

In all discussions of the therapeutic possibilities of streptomycin in tuberculosis, we must view the situation in proper perspective. The ability of streptomycin to suppress the disease is unique and at times apparently remarkable. The limitations of streptomycin are just as real. Because of certain toxic potentialities, its inadequacy in some clinical situations, and the expense of prolonged periods of treatment, the indiscriminate use of streptomycin in the treatment of tuberculosis must be discouraged.

Among the indications for the use of streptomycin in tuberculosis are all forms of hematogenic disease, including generalized miliary tuberculosis and meningitis, the prognosis of which has hitherto been regarded as hopeless. Of twelve patients who had disease of this type and were treated with streptomycin at the Mayo Clinic, four are still living and have been observed for periods of from six to twelve months. Treatment of each of these four patients has been discontinued for from four to six months, and there is not any evidence of reactivation of the disease. Three of these patients who originally presented the classic picture of tuberculous meningitis, are ambulatory and free of symptoms, although two of them have residual neurologic disturbances. One of these two has marked nerve deafness which may be a toxic effect of streptomycin. The other patient has symptoms of cerebellar dysfunction, which are thought to be sequelae of the meningitis.

In treating tuberculous meningitis it is imperative that streptomycin be

* The streptomycin used in these studies was supplied by Merck & Co., Inc., Alibon Laboratories, and The Upjohn Company. From March 1 to September 1, 1946, all supplies were allocated through the Committee on Chemotherapeutics and Other Agents of the National Research Council, Dr. Chester S. Kefauver, Chairman. Since September, 1946, material has been supplied by the Committee on Therapy of the American Trudeau Society.

given both parenterally and intrathecally and as early in the course of the disease as possible. The first five patients who were given streptomycin for tuberculous meningitis at the Mayo Clinic received it parenterally only. Although four of them improved temporarily, all eventually died. It is suggested that the drug be given by lumbar or cisternal puncture, in amounts of from 100 to 200 mg. every twenty-four to forty-eight hours for from four to seven weeks or longer. A single dose of streptomycin is dissolved in 8 to 10 ml. of physiologic saline solution and injected after the withdrawal of 10 to 15 ml. of spinal fluid. In addition, streptomycin probably should be given parenterally for a long period. The four patients with tuberculous meningitis who survived received an average dose of 2 gm. a day by parenteral administration for an uninterrupted period of six months.

The patient who has early tuberculous meningitis usually improves in all respects within one to three weeks after treatment with streptomycin is begun. In our more successful cases it has been impossible to demonstrate tubercle bacilli in the spinal fluid, either by culture or inoculation of guinea pigs, after six to eight weeks of treatment, although their presence was demonstrated prior to treatment in each case. There is a tendency for the spinal fluid to remain somewhat abnormal; for example, the cell count and the concentration of protein are usually higher than normal.

Generalized miliary tuberculosis, likewise, should be treated vigorously; the patient should receive 2 to 3 gm. of streptomycin daily by parenteral administration for several months. Striking, often almost complete clearing of the pulmonary lesion is noted in the roentgenograms within a month or two, but if actual healing is to occur, treatment must be prolonged. One patient in our group who had generalized miliary tuberculosis without meningitis received 2.4 gm. of streptomycin a day for a period of four months. His disease has remained in a state of clinical remission for three months since cessation of treatment. Treatment in three similar but more advanced cases of miliary tuberculosis resulted in temporary improvement only.

In addition to pulmonary lesions of hematogenic origin, pulmonary tuberculosis suitable for treatment with streptomycin includes recent lesions of bronchiogenic dissemination, exudative lesions, and in general all recent but rapidly progressive tuberculosis which is not likely to be brought under control by the usual methods of treatment. Pulmonary tuberculosis has been treated satisfactorily by average daily doses of from 1 to 3 gm., administered parenterally, for a total period of from two to six months. Clinical improvement, including decrease in fever, increase in appetite and reduction in cough and expectoration, is noted early, often within a week or two after administration of streptomycin is begun. Improvement usually can be demonstrated roentgenographically within one to two months. Although closure of pulmonary cavities has been observed roentgenographically during the period of treatment with streptomycin or in the ensuing months, cavities more frequently remain patent, especially if they are thick walled. Likewise the findings in the sputum are changed from positive to negative in only approximately 50 per cent of cases of far-advanced pulmonary tuberculosis with extensive cavitation.

In our experience the patient whose pulmonary tuberculosis has improved during treatment with streptomycin usually continues to improve

after this treatment is discontinued. In only a few cases of pulmonary tuberculosis has reactivation or extension of the disease occurred after cessation of treatment. If the tubercle bacilli recovered from the sputum of these patients are still sensitive to streptomycin *in vitro*, it is likely that the patient will respond to further treatment with the drug. If the strain has become resistant, there is less likelihood of repeating the earlier therapeutic result, but in some instances it has appeared that the resistant strains of bacilli were in the sputum and clinically sensitive strains were in the recurrent lesions.

Use of streptomycin in pulmonary tuberculosis possibly is indicated in conjunction with surgical procedures, such as lobectomy, pneumonectomy and even thoracoplasty. It is hoped that a preoperative course of the drug for one to three weeks and a postoperative course for two to four weeks will improve the patient's condition for operation and decrease the incidence of complications, such as the recrudescence of foci, extension of the disease to new regions and the development of tuberculous empyema. It is reasonable to believe that streptomycin may make surgical intervention feasible more frequently in the treatment of tuberculosis.

A category in which streptomycin has been used with notable success includes tuberculosis of the hypopharynx, larynx and tracheobronchial tree. In our series of ten cases of tuberculosis in these sites lesions have healed promptly and have shown no tendency to recurrence for as long as twenty months after completion of treatment. For these ulcerating lesions of the respiratory tract we have given streptomycin both parenterally and by means of nebulization. For nebulization 500 mg. of streptomycin is dissolved in 20 ml. of physiologic saline solution and the patient is instructed to nebulize 2 ml. every hour for ten hours of the day. Repeated bronchoscopic examinations usually have revealed that healing was beginning within two weeks after treatment was started, and often healing was complete within four weeks. Treatment should probably be continued for seven or eight weeks or longer. It has not yet been determined whether either nebulization of streptomycin or its parenteral administration would be sufficient without the other method of treatment.

In our experience tuberculous draining sinuses have responded well to treatment with streptomycin, even those of long duration which were refractory to all other methods of treatment. These include fistulous tracts due to tuberculosis of the chest wall, abdominal wall and scrotum, and to tuberculous lymphadenitis. We have learned that to prevent recurrence of these conditions it is necessary to continue treatment for several weeks after drainage has ceased, with superficial healing. Streptomycin is given parenterally, and adequate treatment apparently consists of about 2 gm. a day for three or four months.

Other forms of tuberculosis in which encouraging results have been obtained with streptomycin therapy in small series of cases include tuberculosis of the alimentary tract and peritoneum and tuberculosis of bones and joints. Results have been excellent in one case of previously intractable lupus vulgaris. In some other cases presumed to be cutaneous tuberculosis, improvement from treatment with streptomycin has been temporary or questionable.

Streptomycin has been somewhat disappointing in the treatment of

some cases of tuberculosis of the genito-urinary tract. As has been reported previously, marked symptomatic improvement occurs in more than 50 per cent of such cases and the degree of tuberculous bacilluria usually is reduced sharply. In fact in several cases in which we and the urologists at the clinic collaborated in the treatment, the urine became free of *Mycobacterium tuberculosis*, as proved by culture and inoculation of guinea pigs. However, the tendency of tuberculous lesions in the kidney of human beings not to heal is well known and, therefore, the benefits of antibacterial treatment are often only temporary. After weeks or months of treatment or at varying intervals after treatment is discontinued, the tuberculous bacilluria is likely to return. The strain of tubercle bacilli is then usually resistant to streptomycin *in vitro*. It may be worthy of note that some patients continue to have amelioration of their symptoms, even after a resistant strain of *Mycobacterium tuberculosis* appears in the urine. Because of the palliative effect, the possibility of arresting the disease in a small proportion of cases, and the inadequacy of other therapeutic measures, streptomycin is certainly worthy of trial in some cases of bilateral renal tuberculosis and in tuberculosis of a solitary kidney. We do not regard it as a substitute for surgical procedures in cases of unilateral renal tuberculosis, although it may yet prove to be of value in the preoperative and postoperative treatment.

Among tuberculous conditions in which streptomycin is not indicated or in which the indication is less definite, we include all cases in which satisfactory progress is made on a regimen consisting of the usual therapeutic measures. This category would include most cases of minimal pulmonary tuberculosis. Although sometimes lesions in such cases heal exceedingly slowly, it is generally agreed that most minimal lesions in the lung will undergo spontaneous regression or become arrested under favorable conditions. In the few cases of minimal pulmonary lesions in which streptomycin has been used, it would be difficult to prove that streptomycin accelerated the healing process. Inasmuch as the toxicity of streptomycin is being treated as a separate subject in this symposium, it will not be discussed here except to say that the potential toxicity appears to be sufficient to deny the drug to patients who can make a satisfactory recovery without it. The danger is not sufficient to justify denying streptomycin to any patient who is likely to obtain appreciable gains from such treatment.

At present we do not consider chronic fibrocascous pulmonary tuberculosis suitable for treatment with streptomycin unless there is a conspicuous component of more recent exudative disease. Also, our experience has indicated that it is useless to expect streptomycin to be effective in obviously terminal cases of destructive types of pulmonary tuberculosis.

Tuberculous empyema is another condition in which treatment with streptomycin has been disappointing, whether the drug is administered parenterally, intrapleurally or by both methods. Possibly this is due to the fact that purulent empyema fluid is usually frankly acid in reaction, whereas streptomycin is more effective in an alkaline solution. In our series of seven cases, treatment was truly successful in only one case. This patient had tuberculous empyema complicated by a bronchopleural fistula and several draining sinuses of the chest wall. She had been under our observation for four years, in the course of which she had undergone several

surgical procedures without any improvement in her condition. She received 1.2 gm. of streptomycin daily, and in addition a 1 per cent solution of the drug in physiologic saline solution was sprayed into the empyema cavity several times a day. The bronchopleural fistula closed within three weeks, the chest wall healed soon afterward, and it was impossible to recover *Mycobacterium tuberculosis* from the pleural fluid after three months of treatment. At present, ten months after cessation of treatment with streptomycin, the infection has not recurred. When tuberculous empyema is refractory to other methods of treatment, a trial of streptomycin may be worth while. It will be interesting to note the experience of other investigators who may be able to improve on our methods of employing streptomycin in cases of tuberculous empyema.

It must always be emphasized that treatment with streptomycin is not a substitute for rest in bed and sanatorium care, which are still fundamental in the treatment of tuberculosis. Nor can it be expected to supersede collapse therapy and other surgical procedures when these are indicated.

REASONS FOR LIMITATIONS OF TREATMENT WITH STREPTOMYCIN

The limitations of treatment with streptomycin are due to several factors probably inherent in any form of antibacterial therapy for tuberculosis. In the first place, the tissue changes in this disease tend to be destructive and proliferative. Older lesions, especially, are relatively avascular and, therefore, difficult of access for a blood-borne antibacterial substance.

In the second place, streptomycin is predominantly bacteriostatic rather than bactericidal. Youmans found that of a total of fifty-eight human and bovine strains of tubercle bacilli, the growth of 70.8 per cent was inhibited by less than 1 microgram of streptomycin per milliliter of mediums. On the other hand, a concentration of more than 50 micrograms per milliliter was necessary to produce a bactericidal effect on the tubercle bacillus. The behavior of the drug in vivo seems to parallel its activity in vitro. The bacteriostatic action produces a limited suppressive effect on the disease and allows the patient to muster his natural defense forces. If these are sufficient and if the disease process is essentially curable, the ultimate result of treatment with streptomycin probably will be good.

In the third place, the therapeutic potentialities of streptomycin are limited because the duration of bacteriostatic action is limited. After prolonged exposure to streptomycin, strains of *Mycobacterium tuberculosis* may be isolated which are several thousand times as resistant to the effects of the drug as those isolated originally. This problem of drug fastness appears to be paramount at present. The relation of dosage to the factor of resistance has not been determined, but apparently a dose as large as 3 gm. a day will not prevent its occurrence. Fortunately the tubercle bacillus multiplies at a leisurely rate, so that resistance to an antibacterial agent does not become a problem so soon as in the case of other bacteria. From data available at present, the period from the beginning of treatment to the appearance of resistant strains varies from one to several months. Sometimes a resistant strain of *Mycobacterium tuberculosis* may be recovered from a patient and subsequently strains sensitive to streptomycin may be recovered following cessation of treatment. Patients may benefit from a second course of treatment with streptomycin for recurrent tuberculosis.

Whether the problem of resistance to streptomycin can be circumvented remains to be seen. A second antibacterial agent is now being used in conjunction with streptomycin in hope of retarding or preventing development of resistant strains. Variations in dosage schedule are also being employed.

SUMMARY

Streptomycin is the most effective antibacterial agent known for tuberculosis. In vitro it has a marked bacteriostatic action on the tubercle bacillus, and in vivo it tends to exert a deterrent effect on the disease in both animals and man. Its therapeutic value is limited by the fact that after exposure to streptomycin for weeks or months, strains of *Mycobacterium tuberculosis* which are resistant to the effects of the drug may be isolated. Hence streptomycin is of most value in conditions in which temporary suppression of the infection will enable the patient to gain the ascendancy over his disease; healing then occurs by natural processes.

Prolonged arrest of the disease has been achieved by treatment with streptomycin even in cases of hematogenic tuberculosis, including generalized miliary tuberculosis and tuberculous meningitis. For these conditions large doses of streptomycin must be given parenterally for several months, and for meningitis intrathecal injections are imperative also during the early weeks of treatment. Other types of tuberculosis which have responded to treatment with streptomycin include exudative pulmonary disease, ulcerating lesions of the respiratory tract and tuberculous draining sinuses. It has some place in the treatment of bilateral renal tuberculosis or tuberculosis of a solitary kidney. It also is used before and after thoracic surgery for pulmonary tuberculosis. Because of the potential toxicity, use of the drug probably is contraindicated in conditions which will respond satisfactorily to the usual methods of treatment.

Our knowledge of streptomycin is still in a state of flux. Now that the drug is undergoing extensive clinical investigation in many institutions its ultimate place in the treatment of tuberculosis will be determined in time. Experience with this antibiotic agent has proved that tuberculosis is a disease amenable to antibacterial therapy and it is hoped that other usable agents will be forthcoming.

THE ANTIBACTERIAL APPROACH TO THE TREATMENT OF TUBERCULOSIS*

H. CORWIN HINSHAW

The bacillus of tuberculosis is susceptible to the action of several antibiotic substances when the bacillus is growing in cultures; at least one of these, streptomycin, is highly effective in experimental tuberculosis of guinea pigs, and may be regarded as the most effective of all antibacterial substances which have been employed in the treatment of experimental tuberculosis of animals.

* Abstract of paper published in full in the *Journal-Lancet*, 67:131-135 (Apr.) 1947.

Streptomycin is the first antibacterial substance effective against the tubercle bacillus which can be administered to man in doses which are fully equal to those tolerated by experimental animals when computed according to body weight.

The results of treatment with streptomycin in clinical tuberculosis appear to be just those which should be anticipated if the substance has a suppressive effect on the organism of tuberculosis, when actual contact between the drug and the bacterium can be achieved and maintained. Let me emphasize again that these results do appear to be suppressive rather than curative, but, fortunately, the human body has sufficiently potent defensive mechanisms to be able to overcome tuberculosis if only moderate aid be supplied by such methods of treatment as this.

Serious limitations to any antibacterial treatment of tuberculosis are imposed by the pathology of the disease itself, which produces destructive lesions that become irreversible in many organs if treatment is long delayed. Even under these circumstances, there is frequently witnessed a palliative effect of treatment of at least temporary duration.

Other limitations are imposed by the inability of streptomycin to penetrate into the substance of the brain. Patients with miliary tuberculosis have died with evidence of healing of their disease in most organs of the body with the notable exception of lesions in the brain, where the drug has been found to fail in penetration.

Streptomycin therapy probably is further limited as to duration of effective action because of the appearance of drug-fast strains of bacteria after several months of treatment. Fortunately, however, the duration of effective action is sufficient to realize the desired therapeutic effect in many clinical circumstances. In many other clinical circumstances it appears possible that streptomycin may be of sufficient temporary value to permit the institution of radical surgical procedures which could not otherwise have been employed.

The way now appears to be cleared toward steady progress in the development of ever more effective alternative antibacterial agents in the treatment of tuberculosis.

This subject must never be discussed without repeated emphasis of the fact that sanatorium care, collapse therapy and radical surgery very frequently are effective in tuberculosis. These methods of treatment have been fully proved and frequently are applicable to tuberculosis when streptomycin is not. It thus becomes obvious that serious harm to patients might result if they refuse or postpone these known effective types of treatment in the hope that this or some other drug might offer an earlier, more rapid or more permanent result. Very frequently, such patients not only will be disappointed but possibly they may lose all chance of recovery by failing to accept sanatorium care, collapse therapy or surgical treatment when these have been advised.

CHEMOTHERAPY IN MEDICAL CONDITIONS*

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Recent advances in the field of chemotherapy have made available antibacterial agents which are exceedingly effective against many of the infectious diseases. A brief summary of the clinical uses of certain of these antibacterial agents in medical practice may help to clarify a rather confused subject.

SULFONAMIDES

The effectiveness of the sulfonamide compounds in the treatment of certain infectious diseases is well established. In some of these diseases the sulfonamides appear to be more effective than the antibiotic agents now available.

Acute Bacterial Meningitis.—In the treatment of certain types of acute bacterial meningitis the sulfonamides are generally preferred to other available drugs. Sulfadiazine and sulfamerazine diffuse well into the cerebrospinal fluid after oral administration. In those patients who do not respond to the sulfonamides within twenty-four hours or in critically ill patients penicillin should be given both intramuscularly and intrathecally in addition to the sulfonamides. In some cases of pneumococcic and staphylococcic meningitis it appears advisable to use both penicillin and the sulfonamides during the entire course of treatment. If patients seriously ill with influenzal meningitis do not respond rapidly to streptomycin, sulfonamides and perhaps rabbit antiserum should be used as well.

Bacillary Dysentery.—Most authorities feel that the sulfonamides are effective in the treatment of bacillary dysentery if they are given early in the course of the disease. At the present time sulfadiazine or sulfamerazine appears to be superior to the other available therapeutic agents. In some cases it may be wise to give one of the sulfonamides which is poorly absorbed, such as succinylsulfathiazole (sulfasuxidine), in addition to the sulfadiazine or sulfamerazine.

Bacteremia.—In bacteremia due to a variety of organisms the sulfonamides are often effective, and their use should be considered if the organisms are resistant to the antibiotic agents. At times in the treatment of bacteremia the simultaneous use of the sulfonamides and an antibiotic agent appears justified. Sulfadiazine and sulfamerazine should be given in doses sufficient to produce blood levels between 15 and 20 mg. per 100 c.c. of blood.

Infections of the Urinary Tract.—Small doses of sulfathiazole or sulfadiazine are often very effective in eradicating sensitive organisms from the urinary tract. Infections of the urinary tract due to hemolytic streptococci, *Escherichia coli* and *Proteus vulgaris* often respond satisfactorily to sulfathiazole in doses of $7\frac{1}{2}$ grains (0.5 gm.) four times daily. Occasionally infections of the urinary tract due to other organisms respond well also.

Pneumonia.—If patients suffering from pneumonia caused by pneumococci or streptococci do not respond to treatment with penicillin within

* Abridgment of paper published in full in the *Journal of the Missouri State Medical Association*, 44:609-814 (Nov.) 1947.

forty-eight hours, the use of the sulfonamides should be considered. Doses of sulfadiazine or sulfamerazine sufficient to obtain a blood level of 10 mg. per 100 c.c. of blood should be given. The sulfonamides have not been found to be of value in the treatment of primary atypical or virus pneumonia.

Brucellosis.—In some patients suffering from acute brucellosis, particularly those in whom there is bacteremia, the sulfonamides appear to be of value. In some of these patients the sulfonamides appear to induce a remission of symptoms and a return of the temperature to normal. If the sulfonamides are to be used in the treatment of this disease, blood levels of at least 10 mg. per 100 c.c. should be maintained for ten to fourteen days. In our experience at the clinic the sulfonamides have not been of value in the treatment of chronic brucellosis.

Toxicity.—Some of the toxic reactions caused by the sulfonamides are dangerous and many deaths have resulted. The indiscriminate use of the sulfonamides is to be severely condemned.

PENICILLIN

Penicillin has become one of the most important agents used in the treatment of infectious diseases.

Bacteremia.—Bacteremia due to susceptible organisms responds well to treatment with penicillin, providing foci of infection can also be eliminated. Early diagnosis and treatment of bacteremia are essential if desirable results are to be obtained.

Subacute Bacterial Endocarditis.—One of the most gratifying advances in the practice of medicine has been the satisfactory response of many patients suffering from subacute bacterial endocarditis to treatment with penicillin. Adequate dosage is of great importance in the treatment of these patients. Doses of penicillin ranging up to 10,000,000 units per day and more have been necessary at times to eradicate the infecting organism. The intramuscular method of administration may be used in many cases, but in some the continuous intravenous drip method appears to give superior results.

Meningitis.—Meningitis caused by staphylococci and pneumococci should be treated with penicillin. Many authorities believe that the use of the sulfonamides in addition to penicillin is advisable. All patients who have meningococcal or streptococcal meningitis which does not respond to sulfonamides should be treated with penicillin.

Infections of the Middle Ear.—Otitis media and mastoiditis due to sensitive organisms often respond well to penicillin. Even when these conditions are complicated by those of intracranial extension, such as meningitis or sinus thrombosis, the response may be satisfactory.

Pneumonia.—Small doses of penicillin are often sufficient to control mild attacks of pneumonia. Severely ill patients may need large doses. If no improvement occurs within forty-eight hours, or if the patient is critically ill, one of the sulfonamides or antipneumococcal serum may be used simultaneously. Penicillin usually is effective in preventing the development of complications, such as empyema or pulmonary abscess. Even when these complications occur, they often respond to further treatment with penicillin.

Infections of the Genito-urinary System.—In patients with urinary infections which do not respond to sulfonamide therapy penicillin may be effective. Infections due to susceptible organisms, such as *Staphylococcus aureus*, usually respond satisfactorily. Results otherwise usually are disappointing because of the ineffectiveness of penicillin against most gram-negative organisms. Penicillin has been extremely effective in the treatment of gonorrheal infections of the genito-urinary tract.

Infections of the Skin and Soft Tissues.—Furuncles, carbuncles and extensive cellulitis have responded satisfactorily to penicillin. Use of this antibiotic agent systemically, rather than locally, is preferred by most authorities.

Toxicity.—Although penicillin is relatively nontoxic, patients do become rather easily sensitized to it. These sensitization reactions, such as exfoliative dermatitis, may be serious. It is important, therefore, to refrain from using penicillin indiscriminately in the treatment of conditions in which use of the drug is not entirely necessary.

STREPTOMYCIN

Care must be used in the administration of this antibiotic substance, for streptomycin has many peculiarities which penicillin does not possess. With few exceptions, the degree of sensitivity of organisms to streptomycin as determined by *in vitro* studies can be used as an index of the probable effectiveness of streptomycin in the clinical field.

It appears well established that streptomycin is superior to other available therapeutic agents in the treatment of certain diseases.

Tularemia.—Reports from many different investigators attest to the marked effect of streptomycin in the treatment of most patients who have tularemia. The morbidity and mortality from this disease is significantly decreased.

Meningitis.—Meningitis due to *Hemophilus influenzae* usually responds well to streptomycin. This antibiotic agent should also be considered in the treatment of meningitis due to other organisms which are sensitive to streptomycin.

Bacteriemia.—Bacteriemia due to certain gram-negative and gram-positive organisms responds well to treatment with streptomycin if the organism is of a sensitive strain. Streptomycin is often effective in the treatment of bacteriemia caused by organisms which are resistant to penicillin.

Infections of the Genito-urinary Tract.—Infections of the urinary tract due to certain susceptible gram-negative organisms respond well to treatment with streptomycin, but the results in the routine treatment of urinary infections with streptomycin are disappointing. The best results appear to be obtained when the organism of infection is either *Proteus ammoniac* or *Aerobacter aerogenes*. Poor results usually are obtained when a foreign body or obstruction is present in the urinary tract. Streptomycin is most effective in alkaline urine.

Infections of the Respiratory Tract.—Encouraging results have been obtained in the treatment of some types of pulmonary disease with streptomycin. Pneumonitis, particularly that caused by *Klebsiellae pneumoniae* or

Hemophilus influenzae, may respond to treatment with streptomycin. Empyema due to sensitive organisms occasionally responds well.

Tuberculosis.—Evidence is accumulating which shows that streptomycin has a limited suppressive action on infections due to the tubercle bacillus. In many cases of predominantly exudative tuberculosis of the lungs the immediate results have been satisfactory. Tuberculous lesions of the larynx and tracheobronchial tree usually have healed under treatment with streptomycin. Chronic draining sinus tracts may close within a few weeks after the administration of streptomycin is started. However, fatality rates continue high in cases of tuberculous meningitis and miliary tuberculosis in spite of treatment with streptomycin. In renal tuberculosis actual healing has been observed only rarely. The place of streptomycin in the treatment of tuberculosis has not been fully determined. However, it appears that it may be a useful adjunct when combined with standard methods of treatment.

Toxicity.—No serious uncontrollable toxic reactions have been encountered from the use of streptomycin. However, irreversible neurotoxic effects on the eighth cranial nerve may occur if treatment with streptomycin is prolonged.

FOOD AND HEALTH*

RUSSELL M. WILDER

He or she who lives successfully with diabetes soon learns some very simple dietary rules: (1) to eat only enough to satisfy daily needs and never to gormandize, even on Thanksgiving Day; (2) to eat sparingly of foods which contain much starch or sugar; in any case, to take foods or drinks with quickly available carbohydrates such as fruits, and so forth, only at the end of meals and, except in order to treat an insulin reaction, never between meals; (3) to avoid foods of unknown composition such as canned fruits packed in syrups, cakes, pies and confectionery, and (4) to eat at regular times three times a day; or, if between-meal feedings are part of the dietary plan, to have these snacks at regular times.

Not so readily learned is another very important rule. This is to choose health-giving foods. Not only diabetic patients but everyone ought to keep this rule.

Many, but not all, physicians with experience in diabetes instruct their patients to weigh their foods or at least to measure what is eaten. For this measuring, use is made of standard measuring cups and spoons and other simple gadgets, such as models of a slice of bread of a standard size. A measured diet of this type can be planned to supply a fixed amount of sugar-forming food at every meal. Its calories can be counted and the amount and kind of protein can be regulated. Also if a measured diet is well planned and the foods are properly prepared the patient is assured of receiving the several vitamins and minerals that he requires. The food

* From the American Diabetes Association Forecast. 1:9-12 (Mar.) 1948.

eaten must be wisely chosen to insure that everything necessary for healthiness, obtainable from food, is actually included in the diet.

Many people fail to eat health-giving foods. Physical examinations, as well as estimates of food consumption based on dietary surveys, have uncovered deplorably bad food habits in large segments of the population. Many persons, even in our supposedly well-fed U. S. A., are not well fed. Some fail to get enough of one or several of the various vitamins necessary to keep fit. Many, especially those who dislike milk, do not get enough calcium. The protein intake sometimes is inadequate. A common error is to take too many calories, more food energy than is needed. This results in overweight, which not only is a common cause of diabetes, but if a person already has diabetes is sure to make the diabetes worse. Overweight also leads to other grave disorders. A strange but not uncommon observation is the association of frank obesity with evidence of ill-health due to lack of some important vitamin.

Unwise selection of food provokes poor health in diabetic patients and in others. Numerous observations like the following have forced this on my consciousness. A little patient from South Dakota, a girl eight years old, was brought to me because of diabetes. She was thin and weak, with poor muscles and dry, scaly skin. Sugar had been found in the urine six months before. A diet had been ordered but no insulin had been given. The child received the usual attention, which included insulin and a proper diet. She rapidly recovered weight and strength, and was dismissed with directions to the parents to bring her back again within a year. The parents did not follow this advice implicitly, but came back two years later, bringing not only the little diabetic patient but three more of the six children in the family. Now the interesting observation is this: that the diabetic girl after two years on her diet was healthier in every way, except for diabetes, than the two brothers and the sister who accompanied her. The diet that my colleagues and I had prescribed for her provided milk, cheese, eggs and meat together with garden greens, tomatoes and citrus fruits. The two brothers and the sister, on the other hand, had continued eating the foods to which this family was accustomed: very little meat, no milk, very little vegetable except potato, much white bread (and it was not "enriched"), much sugar in the form of sweetened desserts and candies. The diabetic girl was taller and more rugged than the sister, who was two years older. Her eyes had much more sparkle, her hair was glossier and her skin was smoother. The sister's lips were chapped; hers were not. In the corner of the sister's mouth were tiny open sores. Scars of former sores were present, also, in the corners of the mouth of one of the two brothers. These boys were underheight for their age and underweight for their height. We asked about school performance. The older sister and the boys were laggards in school; the patient led her class.

Diets adequate in quantity but poor in quality sometimes bring on actual disease; scurvy, beriberi and pellagra are examples. Much more frequent is a state of ill-health not severe enough to prompt a visit to a physician, yet detracting greatly from efficiency. The two brothers and the sister of my little patient were in this state of semihealth.

Recently revived from the writings of Pavy in 1875, before vitamins were known, is the following. I include it here because Frederick William

Pavy, an English physician who lived from 1829 to 1911, was a pioneer in the study of diabetes:

"Upon the supply of a proper quantity and quality of food the maintenance of health and life is dependent. The records of this and other nations have from time to time afforded bitter evidence of how intimately disease and mortality are associated with the supply of food. *Plague, pestilence and famine* stand associated together in the public mind; and through an imperfect knowledge of the principles of dietetics the most calamitous results have sometimes occurred."

Thus whatever dietary plan is chosen by the diabetic patient, whether foods are weighed or not, attention must be paid to the nutrients which foods provide. The calories (food energy) must be sufficient and not excessive. The protein should be ample and with not less than half of it coming from meat, milk, cheese or eggs. The supply of calcium and iron should be liberal and the vitamins must be fully represented. Unless milk is used the calcium supply is likely to be skimpy. Unless green vegetables and meat are taken the amount of iron may be insufficient. Without green and yellow colored vegetables, or with too little butter or fortified margarine, the amount of vitamin A may be inadequate; and without orange or other citrus fruits, tomato or a liberal amount of raw cabbage, vitamin C may be missed. Thiamine, riboflavin, niacin and the several other vitamins of the vitamin B family present a special problem for the diabetic patient. His requirement for them may be on the high side as compared to the requirements of others. I get this impression—it is not a proved fact—from observing what appears to be increased healthiness and vigor after supplementing diets for diabetic patients, which were already good diets, with an extra supply of B vitamins. They are given preferably in the form of two level tablespoonfuls daily of brewers' yeast. However, whether yeast is used or not, the diabetic patient ought to make quite sure that the bread he takes is either real *whole* wheat bread or enriched bread. Just because a bread is brown does not mean that it is whole wheat. Whole wheat is a good source of the B family vitamins. Enriched white breads and enriched white flours provide *thiamine, riboflavin and niacin*, as do whole wheat breads and whole wheat flours, and while they are not as satisfactory as whole wheat breads or whole wheat flours they are definitely to be preferred to white breads or white flours which are not enriched, the latter being very poor in vitamins.

The diabetic patient more than others needs to pay attention to these matters, but what is good for him is good for others. "How do you manage to stay on your diet so well?" asked a dietitian.* "I do not only stay on my diet," the patient answered, "but the whole family has gone on the same diet with me. Strange to say we are all in better health today than we were two years ago." See to it then that your diet provides at least a pint of milk a day, preferably a quart, at least four eggs a week, preferably one a day, butter, or if oleomargarine is used in place of butter it should be fortified with vitamin A, *one portion of meat daily, if possible taking liver* once a week, real whole wheat bread or enriched bread, at least one cooked green or yellow vegetable, a daily salad of a raw leafy vegetable, and at least one serving daily of a citrus fruit or tomato or raw cabbage.

* Sister Maude Behrman, "The Picture of Health," *Diabetic News*, June, 1946.

THE NUTRITIONAL QUALITY OF FOOD AND STANDARDS OF IDENTITY*

RUSSELL M. WILDER

By nutritional quality I refer in no way to the size, shape, taste, appearance or cost of any food, but rather to the value of the product for the nourishing of people.

The science of nutrition has advanced in recent years to the point where human needs for calories, amino acids, calcium, iron and several vitamins of conspicuous significance are reasonably well known. Also accumulated is a vast amount of reliable information about the composition of the common foodstuffs, in their natural forms and in their condition after processing and storage. Likewise many surveys of food consumption and medical examinations of samples of the population have shown that many persons in this country are obtaining less than what is needed for good health; less, that is, of several of the nutrients essential for good health. Diets are adequate in calories with very few exceptions, but missing not infrequently are adequate amounts of certain vitamins and amino acids, of calcium, and of iron.

INEFFECTIVENESS OF EDUCATION

A major reason for our failure in this country to achieve a better level of nutrition is that the food environment is anything but satisfactory. Foods sell for their taste appeal or for the attractiveness of their appearances, and the public finds itself surrounded with grocery shelves full of products which are less nutritious than they might be. Educating people in what to buy is slow, and in the meantime millions are denied the blessing of the better health they would enjoy if their diets were more nourishing. Physicians for a hundred years have inveighed against denatured foods and teachers trained in the science of nutrition have urged the greater use of what are called protective foods—milk, whole grain cereals, fruit and leafy green and yellow vegetables. The result is disappointing. Even with the tremendous effort of the nutrition campaign conducted in and since the recent war years the lesson fails to reach large segments of the population. People eat what pleases them with little thought about what food does to them. Appeals to health made to the healthy or to those who, although perhaps less healthy than they could be, consider themselves healthy, are largely ineffective. Moreover such appeals are made in competition with powerful advertising which appeals to taste, and for every person instructed by a teacher of nutrition, food industry by advertising reaches people by the thousands. Not that taste is unimportant nor that all this advertising is pernicious from the standpoint of nutrition. Due credit can be given to the effort of food industries to spread the gospel of good eating, and for this co-operation in the campaign for better nutrition conducted during the war, without weakening the main argument that foods sell for their taste and appearance and not for the nutrients they contain.

If prevention of the ill effects of poor diets is as important a public health

* Abridgment of paper published in full in the *Food, Drug and Cosmetic Law Quarterly*, 2:75-84 (Mar.) 1947.

measure as is believed, how can it longer be considered reasonable to permit the marketing of foods which fail to carry the nutrients which people ought to find in them? Surrounded as consumers are with inferior foods, the fraction of the population which can be educated to exercise the discrimination necessary to select a good diet must be very small. On the other hand, if the nutritive quality of the more important foods could be assured by regulation, the problem would be nearly solved. People then would find themselves in a nutritional environment in which it would be difficult to go wrong, instead of, as now, in a situation in which it is difficult to go right.

IMPERFECTIONS OF THE FOOD SUPPLY

Experiments performed under my direction confirm the views of many others that the present food supply is unsatisfactory. In these experiments measured foods, of which the composition had been determined by analysis, were fed to volunteers. The amounts of each food given were such as to make the diet simulate a hypothetical average American diet. In other words, the calories provided by white flour (unenriched) represented 25 or 30 per cent of the total calories consumed, and calories from other vitamin-poor foods, such as sugar, polished rice, cornstarch, corn meal and the like, provided another 15 or 20 per cent of all the calories. This diet contained a fair portion of meat, butter, a small salad of fresh vegetables, as well as processed fruits and vegetables, and yet despite the presence of these amounts of the "protective foods" the subjects who lived on the regimen for several months developed serious disabilities. The disabilities could be corrected by selecting vegetables and fruits which contained more vitamins or by using bread made with enriched or whole wheat flour. The point is that with the flour unenriched a diet containing as much white bread and sugar as people commonly consume can only be made adequate by a very wise selection of the balance of its foods. In point of fact, with consumption of flour and sugar at present levels, even if the flour is of the enriched or whole wheat flour variety, the nutritional situation in this country is one in which the necessity for discriminating diet planning is greater than can be expected of the average citizen.

The major current problems of nutrition have been created by commercial processing of foods. Flour, corn meal and sugar have been the worst offenders in the Occidental countries because of the magnitude of their contribution to the diet. The bread grains represent a most important source of certain vitamins, but in converting wheat into white flour from 86 to 90 per cent of one of these vitamins (vitamin B₁, thiamine) is lost and from 60 to 80 per cent of another vitamin (niacin) is removed. Minerals are also lost; chief of them is iron. The answer to this white bread problem is either the preservation or the restoration of these nutrients.

Rice contributes as much as 80 or 90 per cent of the calories of the diets of some populations of the Orient. It also is used extensively by some portions of the American population, notably in the Philippine Islands, in Puerto Rico, and in certain communities of the lower part of the Mississippi Valley. Extensive milling, so-called polishing, removes the vitamins from rice and this processing is responsible for untold human suffering. It is high time for action in this matter. It is nearly fifty years since proof

was brought by Christian Eijkman that commercial processing of rice was the cause of the "epidemic" beriberi of the Orient. In some parts of the world beriberi is responsible for more than a fourth of all disease. A standard of identity and quality for rice which included the requirement of a certain quantity of thiamine would solve this problem.

Methods of canning as now provided by the industry are excellent for the most part, but in some canneries control is lacking and thus some foods are grossly injured in their canning. An example is tomato juice which is much in demand, not only because of its pleasing taste but also because the public or a part of it has learned to recognize the tomato as a good source of the anti-scurvy vitamin, ascorbic acid (vitamin C). Yet among thirty samples of tomato juice tested for their content of this vitamin at the Connecticut Agricultural Experimental Station, only three contained an amount equal to what may be regarded as average for fresh tomatoes. Six samples contained 15 mg. per 100 gm. or less, representing only 60 per cent or less of what should be expected in tomatoes. At the same laboratory analyses were made of forty-nine samples of orange drinks. The results showed that few of these drinks contained significant amounts of vitamin C and that twenty-nine had a vitamin C potency of less than 2 per cent of fresh orange juice. This is a matter of great importance because orange drinks are associated in the minds of the consumer with a high content of vitamins, and the teachers of nutrition are teaching that it is difficult to prevent deficiency of vitamin C without including citrus fruits in the diet.

A problem even more serious than that created by canning is presented by the processing of foods by dehydration. This method for preserving perishable commodities promises to become very popular. Costs of transportation can be minimized by dehydration to the advantage of the consumer. However, unless the dehydration of the food is done with care, heat sensitive constituents are lost. This industry, unfortunately, is not well organized. Many newcomers in the industry lack knowledge of the difficulties involved and possess inadequate facilities for controlling their procedure.

EXISTING FOOD CONTROL

Before the passage of the Federal Food and Drug Act of 1906 many so-called pure food bills were introduced in one or the other houses of Congress. They were promptly killed, being smugly looked on, as Dr. Wiley told, as the work of cranks and reformers without much business sense. However, the evolutionary progress to attainment of existing regulations, from the effort to prevent adulteration to the law against adulteration and misbranding, to the Food, Drug and Cosmetic Act of 1938, which enabled the establishment of administrative regulations, has largely been made possible by the support of the businessmen in the industries involved. The question which I now would raise involves a further step in this evolution of protection, not only for consumers but also for enlightened industry.

Although the pure food law of 1906 was aimed at preventing adulteration and mislabeling and the essence of the Act of 1938 was to strengthen the protection of the consumer from exploitation, yet even under the Act of 1938 nothing has been done—some hold that nothing can be done—to

prevent exploitation of the consumer by the destruction of nutrients or extraction of values which the consumer frequently supposes to be present in the product which he purchases.

It is not for me, a physician and little acquainted with law or administration, to prescribe the means for accomplishing what so obviously is required to improve the *nutritive quality* of the food supply. Existing Federal legislation, if liberally interpreted by the courts, may permit the establishment of standards of *nutritive quality* by regulation. Section 401 of the Food, Drug and Cosmetic Act provides: "That whenever in the judgment of the Secretary (Administrator) such action will promote honesty and fair dealing in the interest of the consumer he shall promulgate regulations . . . establishing for a food . . . a reasonable standard of identity, (and) a reasonable *standard of quality*."^{*} In my opinion the court could justly interpret the words "standard of quality" as implying a standard of *nutritive quality*. However, among the foods for which standards of nutritive quality are needed, as I have pointed out, are dried fruits, dried vegetables and butter, whereas the language of Section 401 of the Food, Drug and Cosmetic Act goes on to state, "provided that no^{*} definition and standard identity and no^{*} standard of quality shall be established for fresh or dried fruits, fresh or dried vegetables or butter. . . ." In the light of this restrictive language some revision of the act would be required to effect improvement of these articles.

Decisions as to what foods are most in need of improving and how their improvement is to be effected should be based on advice obtained from experts in the science of nutrition. The Federal Government now has at its disposal, available at all times for consultation, the Food and Nutrition Board of the National Research Council. This board is composed of physicians and scientists selected from among authorities in the science of nutrition. The membership, for the most part, comes from the leading universities of the country, and policies having to do with the nutritional aspects of food could be wisely and impartially guided by such a body. Precedent for the suggestion can be found in Chapter V of the Food, Drug and Cosmetic Act. Although, as I have pointed out, this act as heretofore interpreted does little to prevent the marketing of foods that fail to measure up to any standards of nutrient quality, it deems a drug to be *adulterated* (Section 501b) if "its strength differs from or its quality . . . falls below" certain standards. Furthermore, the standards recognized are those established by authorized scientific bodies and the responsibility of these bodies extends to designating the tests or methods of assay for determining whether the strength, quality or purity of drugs meets these standards.

ACTIONS NOW DESIRABLE

The Food and Nutrition Board of the National Research Council, the Council on Foods and Nutrition of the American Medical Association, the American Public Health Association and the Association of State and Territorial Health Officers, to judge from recent actions of these several authoritative bodies, would probably support the issuance of the standards of nutritional quality suggested below for each of the following foods:

* *Italics mine*

White Flour.—A standard of identity which would require that all white flour which moved in interstate commerce contain not less than the amounts of thiamine, riboflavin, niacin and iron which are required for flour now identified as enriched flour. (Such a regulation might encounter objection from commercial bakers, many of whom prefer to add the vitamins and iron to their dough. However, flour sold to them could be excepted without loss of the objective, provided enrichment of their bread was mandatory.)

Bread and Rolls.—A standard of identity which would require that all bread and rolls which contained much white flour contain not less than the amounts of thiamine, riboflavin, niacin and iron which, in the contemplated but not yet promulgated standard of identity of breads, is required for enriched bread.

Olcomargarine.—A standard of identity which would require a content of not less than 9,000 (or perhaps 15,000) units of vitamin A per pound. (The present standard does not require but permits the addition of 9,000 units of vitamin A per pound as an optional ingredient.)

Table Salt.—A standard of identity which would require a content of potassium iodide or its equivalent equal to that now mandatory for so-called iodized salt.

FINAL COMMENTS

For each of the products I have named the industries involved have evinced approval of regulation requiring the nutritional improvements suggested and opposition to such regulation, should it come, from other sources, ought not to influence a court that sought in interpreting the Act "to give the greatest possible protection to consumers" and I might add "to enlightened industry."

Bearing on the question of authority for such regulations is the opinion delivered by Mr. Chief Justice Stone in the case of *The Federal Security Administration vs. The Quaker Oats Company*, 318 U.S. 218. He said: "The standards of reasonableness to which the Administrator's action must conform are to be found in the terms of the Act construed and applied in the light of its purpose. Its declared purpose is the administrative promulgation of standards of both identity and quality in the interest of consumers." The Chief Justice further pointed out that "both the text and the legislative history of the present statute plainly show that its purpose was not confined to a requirement of truthful and informative labeling. False and misleading labeling had been prohibited by the Pure Food and Drug Act of 1906. But it was found that such a prohibition was inadequate to protect the consumer from 'economic adulteration,' by which less expensive ingredients were substituted, or the proportion of more expensive ingredients diminished, so as to make the product, although not in itself deleterious, inferior to that which the consumer expected to receive when purchasing a product with the name under which it was sold. The remedy chosen was not a requirement of informative labeling. Rather it was the purpose to authorize the Administrator to promulgate definitions and standards of identity under which the integrity of food products can be effectively maintained."

I suggest that the word "integrity" is inapplicable to any food from which important nutritional values have been removed in processing unless these are restored.

I named above four foodstuffs, white flour, bread, oleomargarine and table salt, for which the time has come, in my opinion, for regulation of nutritional quality by requiring a content of certain nutritional values. Support from physicians, from nutritionists and from industry for regulation of other foods should also be obtainable as the need is clearly shown in every instance and adequately demonstrated in the public hearings required by the Act before the promulgation of any regulation. Thus one by one each of the foods which contribute importantly to the American diet could be effectively improved to the great advantage of consumers and elevation of the nation's strength and vigor "within our time and generation." Freedom from want of food cannot be won without attention to the nutritional quality of the food provided.

A SELF-REGULATING FEEDING PROGRAM FOR INFANTS*

C. ANDERSON ALDRICH AND EDITH S. HEWITT

The care of 668 babies was supervised in well-baby clinics from the time of their dismissal from the hospital to go to their homes, until their first birthdays. All of these infants were put on a self-regulating regimen designed to allow the babies free choice as to intervals of feeding and amounts of food, although the kinds of foods included in the menu were prescribed. The records of these babies were studied with respect to the feeding intervals chosen by the babies throughout the first year and as to their appetite and attained stature at one year of age. The word "stature," is employed in this paper in its meaning of "development" or "growth," which embraces both height and weight.

The feeding intervals during the first month of life were classed as irregular, two-hour, three-hour, four-hour, four meals daily and three meals daily.

The babies chose to lengthen their feeding intervals gradually so that the average at various months agreed fairly closely with the intervals usually prescribed by physicians. However, a large majority of babies desired an interval of less than four hours in the first two months of life and our figures show that a rigid routine, even if regulated to fit the average baby at each age, will leave a large group of infants poorly adjusted as far as timing is concerned.

At one year of age, 91 per cent of the babies had automatically placed themselves on a regimen of three meals a day.

At one year of age, the appetites of 92 per cent of the babies were excellent, those of 7 per cent of the babies were of borderline character and those of less than 1 per cent of the babies were poor.

The attained heights and weights of the babies at one year of age compared favorably with the generally accepted standards, 29.4 inches (74.67 cm.) and 21.8 pounds (9.9 kg.) respectively.

* Abstract of paper published in full in the Journal of the American Medical Association, 135:340-342 (Oct. 11) 1917.

SOME FACTORS WHICH INFLUENCE THE DURATION OF BREAST FEEDING*

MILDRED A. NORVAL

The duration of breast feeding in a group of 462 women was investigated in relation to certain factors in both the mothers and their infants. After women reach the age of thirty years there is a decrease in the adequacy of the supply of breast milk, particularly among those delivered of their first living child. As was evidenced by the number of infants who were being breast fed at the time of dismissal of their mothers from the hospital, the age of the mother did not affect the duration of breast feeding, once it had become established. Parity did not influence the supply of breast milk. Those women who lived in the country breast fed their infants 0.8 months longer than those who lived in a town or city. As the number of days before onset of engorgement increased, there was a decrease in the adequacy of breast feeding, seen both on dismissal of the mother from the hospital and as a decrease in the duration of breast feeding. It is an interesting observation that, on the one hand, those women who had engorgement of grade 1 and, on the other hand, those who had engorgement of grade 4, were less able to breast feed their infants than were those women who had engorgement of grade 2 or grade 3. The birth weight of the infant did not influence the adequacy of the supply of milk or the duration of breast feeding.

CLINICAL OBSERVATIONS ON STARVATION EDEMA, SERUM PROTEIN AND THE EFFECT OF FORCED FEEDING IN ANOREXIA NERVOSA†

JOHN M. BERKMAN, JAMES F. WEIR AND EDWIN J. KEPLER

During and immediately after World War I opportunities and methods were available for the first time for the study of the effects of inanition on the human subject on a large scale. It was observed that starvation often was followed by edema, and in about half of the subjects examined the concentration of the serum proteins was decreased. It also was observed, but not so often stressed, in the voluminous literature that appeared, that under apparently identical circumstances normal values for serum proteins might be obtained and that definitely subnormal values were not necessarily associated with edema. Possibly because the first-mentioned observations were more in keeping with Starling's theory of formation of edema, emphasis was placed on the importance of the serum proteins in maintaining a dynamic equilibrium between the intravascular and interstitial fluids. Starling's concepts were buttressed when it was shown in animals that edema occurred if the level of the serum proteins was reduced either by

* Abstract of paper published in full in the *Journal of Pediatrics*, 31:415-419 (Oct.) 1947.

† Abridgment of paper published in full in *Gastroenterology*, 9:357-390 (Oct.) 1947.

diets low in protein or by plasmapheresis. Consequently, it was generally thought and taught that hypoproteinemia was the crucial factor in the production of starvation edema.

During and following World War II, however, emphasis frequently was placed on the absence of correlation between starvation edema and the concentration of the serum proteins. The plasma proteins were studied intensely by new and more precise physical and chemical methods. As a result, Starling's concepts have been thoroughly scrutinized and sometimes discredited.

Comparatively few cases of anorexia nervosa have been reported in which edema has been observed and values for serum proteins recorded. In some of the cases reported the coexistence of anemia and edema has been noted. In 1930 one of us reported on 117 cases in which a diagnosis of anorexia nervosa had been made at the Mayo Clinic in the thirteen years from 1917 to 1929, inclusive. Edema was noted in only three cases in this series and appreciable anemia in only five. This low incidence of both edema and anemia probably results from two factors: (1) edema was not looked for routinely and (2) serial examinations of the blood were not made.

The literature on anorexia nervosa would indicate that in this condition edema, anemia and decreased concentration for serum proteins may occur, but occur infrequently, and that the degree of emaciation is comparable in severity with that seen during wars and famine.

PURPOSE

For a number of years we have been interested in the manner in which patients who were emaciated as a result of anorexia nervosa have gained weight and in 1943 one of us called attention to a peculiar weight curve observed in a number of instances in which considerable weight had been gained. When an obese patient suddenly restricts his caloric intake, weight is lost rapidly during the first week. Subsequently, the weight remains stationary for a time and then decreases progressively. The initial rapid decline probably represents in part loss of extracellular fluid. The curve of weight gain in cases of anorexia nervosa appears to be the reverse. A satisfactory initial gain may occur for a week or even ten days. This phase is followed by another which lasts a week or ten days or longer, during which little if any weight is gained. At the end of this period, however, the patient, without any increase in caloric intake, will begin again to gain weight. It was suggested that the initial rapid gain in weight might be explained by retention of electrolytes and water and that during the phase in which no gain in weight occurred, excretion of water might be balanced roughly by an actual storage of flesh, which could be fat or muscle or both.

In 1945, one of us pointed out that patients who respond exceptionally well to dietary treatment may have edema of the feet and ankles at the end of the first week or ten days of treatment; that the edema may not be noticed unless particularly looked for, and that it develops concomitantly with the initial gain in weight. In some instances the edema may be so extensive that the patient cannot wear the shoes that she has worn previously. In 1945 it was reported also that the values for serum proteins were normal in these cases.

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nervosa. In these studies particular attention was paid to the level of the serum proteins and to the albumin-globulin ratio before and during treatment with a diet high in protein, calories and vitamins.

Although it is the purpose of this paper to point out the relationship of the serum protein, edema and weight curve during dietary treatment and not to emphasize the treatment itself, for the sake of clearness the dietary treatment employed will be mentioned briefly.

DIETARY TREATMENT

When cachexia is extreme, treatment must be cautious and undertaken with the understanding that little or no improvement can be expected for some time. Aggressive treatment of patients who have extreme degrees of emaciation may prove disastrous. In the presence of extreme emaciation the necessity for tube feeding or for daily intravenous administration of fluids is a sign of danger and should be proceeded with cautiously. Results in this situation should never be predicted.

Since 1938 we have employed a dietary regimen somewhat similar to that recommended by Farquharson. Its basic principle is a gradual increase in the caloric content and bulk of the diet. These patients either will not or cannot tolerate abrupt changes in their dietary habits. They frequently say, "My stomach has shrunk." Sudden increases in the bulk of the diet are followed by upper abdominal distress, lack of confidence and co-operation, and consequently failure. Although the caloric value of a high-protein diet does not reflect accurately the amount of bulk in the diet, nevertheless, increasing a high-protein diet by the addition of 300 calories at a time will gradually increase the bulk of the diet. A rough estimate of the patient's daily caloric intake prior to arrival at the clinic is made. To this amount is added 300 calories. The patient is given a high-protein, high-vitamin diet based on that number of calories (usually 1,300 to 1,500 calories or less) and is asked to eat everything served her. For the first few days the patient may complain of distress and a sensation of fullness. However, after several days these symptoms gradually become less. In five or six days the caloric content of the diet is increased by another 300 calories. For the next two or three days discomfort is again experienced; however, the symptoms again become less. This procedure is repeated until the intake reaches 3,200 calories. These patients experience far less distress eating this amount of food than they had experienced for the initial diet which was based on 1,300 calories or less.

The food values of the diets as used in caloric increases are as follows:

Carbohydrates, gm.	Protein, gm.	Fat, gm.	Calories
115	71	60	1,300
150	73	79	1,600
187	75	93	1,900
219	80	114	2,200
245	83	135	2,500
295	91	185	3,200

Farquharson used the method of gradually increasing the caloric value of frequent feedings. In this method when the diet valued at 3,000 calories is reached and gain in weight is evident, the frequency of the meals is gradually lessened and the variety of food is increased.

CASES STUDIED AND METHODS USED IN REPORT

Thirty-one patients having anorexia nervosa who came to the Mayo Clinic from January, 1941 to May, 1947, inclusive, were studied. Two were admitted during 1941, one during 1943, three during 1944, nine during 1945, thirteen during 1946 and three during the first two months of 1947. Three cases will be presented in detail.

The thirty-one cases have been classed roughly into three groups. In group 1 are included the cases in which the patients' lowest weights were from 41 to 61 per cent of their standard weights and all but one patient had edema. This one patient was included in this group as she doubtless would have had edema if she had remained for treatment. In group 2 are the cases in which the patients' lowest weights were not much less than the standard weights. These patients also exhibited edema. In group 3 are the cases in which edema was absent exclusive of the one in group 1.

Data to be presented have been restricted to those observations that bear directly on the subject under discussion. All mention of negative or noninformative laboratory tests has been omitted as well as the results of more specific laboratory tests. In each case the caloric intake of food had been restricted and as far as could be determined this restriction was commensurate with the reduction in weight that followed. In some instances it was possible to determine the immediate psychic trauma which led to the voluntary restriction in the intake of food. In other cases it was not. Psychiatric examinations usually were not conducted. By and large we have thought that this type of study had best be reserved until the patients have recovered from the debilitating effects of the illness. Premature efforts to probe the peculiarities of the personalities of these patients often induce an antagonistic attitude which renders somatic therapy difficult. Subsequently, psychiatric examinations usually are unnecessary except for academic interest. Nevertheless, in all cases psychic therapy of a sort was employed. The patient was told that the somatic clinical picture was the direct consequence of the inadequate intake of food rich in calories and that she would recover if she co-operated. All of the patients were studied carefully to exclude the presence of other conditions, such as the cachexia which is sometimes reported to be associated with organic lesions of the pituitary body and the adjacent hypothalamic regions, sprue, regional ileitis and other diseases of the gastro-intestinal system.

Detailed descriptions of the physical status of the patients have been omitted deliberately from this report. The photographs speak for themselves and give evidence of great emaciation and in a number of cases of hirsutism. Pitting edema, except when it is extensive, is difficult to show photographically. The "infantile" type of uterus and glazed atrophic vaginal mucosa, such as occurs when estrogenic stimulation is wanting, was present in all cases.

In severe and typical cases the following laboratory abnormalities can be expected: The basal metabolic rate is subnormal; the glucose tolerance curve is flat throughout a three hour period; the rate of urinary excretion is decreased when large quantities of water are ingested, and urinary excretion of gonadotrophic substances, 17-ketosteroids and estrogenic substances is absent or minimal. In a few cases in which we have studied it, the urinary excretion of the "cortin-like substance," determined by the

chemical method proposed by Talbot and his associates, usually was abnormally low or entirely absent although in one instance abnormally high values were found. All of these studies were not conducted in each case, and for the sake of brevity none of the results are incorporated in this report. The over-all picture from the laboratory point of view is that of severe but reversible anterior pituitary insufficiency. It is this reversibility which in the last analysis distinguishes anorexia nervosa from the cachexia that sometimes occurs in cases of pituitary necrosis, pituitary tumor and allied intracranial lesions.

GROUP 1

The first three cases are reported in detail and a brief résumé of the salient points in the first seven cases is given in table 1.

Case 1. Extreme Emaciation; Absence of Edema; Normal Values for Serum Protein.—On September 19, 1943, a married woman, aged twenty-four years, came to the clinic because of progressive loss of weight which had been occurring for seventeen months. From 1938 at the

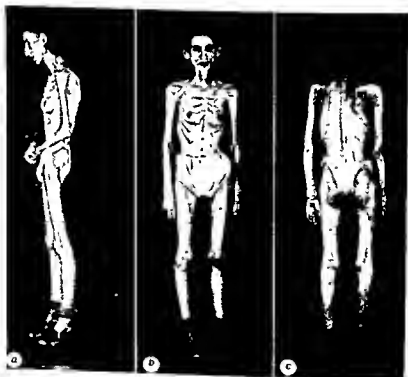


Fig 124 (case 1).—a, b and c September 20, 1943, at time of admission. Patient weighed 50 pounds.

age of seventeen years until April, 1944, she had weighed 122 pounds (55.3 kg). She then had begun to lose weight rapidly. During the next twelve months she had lost 72 pounds (32.7 kg) and for the five months just prior to her admission, her weight had remained stationary at 50 pounds (22.7 kg). She had been amenorrheic since March, 1944. Her height was 5 feet, 2 inches (157.5 cm). The standard weight for this age and height is 121 pounds (54.9 kg). These figures show her at 50 pounds to be weighing 41.3 per cent of the standard weight.

TABLE 1
GROUP 1: PATIENTS STUDIED IN DETAIL, MOST OF WHOM EITHER HAD EDEMA OR ACQUIRED EDEMA

Case	Age, years	Height	Weight, pounds				Lowest weight, per cent of standard	Edema of lower extremities, grade before and during treatment		Serum proteins, gm per 100 c c		
			Standard	Usual*	Lowest	Loss	Duration of loss, years	Before	During	Total	Albumin	Globulin
1	24	5' 8"	121	116	50	66	3½	0		7.9†		
2	18	5' 5½"	146	114	51	65	4½	1	0	8.41 8.21 8.61 8.16	4.40 4.04 5.10	1.77 1.73 1.68
3	23	5' 4"	119	115	62	56	7	1	8+	6.41 5.11 6.86 6.01	4.02 3.13 5.55	2.37 1.68 3.53
4	35	5' 6"	147	146	76	62	5	1	5	6.41 5.91 5.71 6.51	4.18 3.80 4.15 4.12	2.60 1.43 1.51 2.17
5	18	5' 2"	117	146	71	55	2½	6	10	5.71 6.71 6.01 7.16	4.42 4.16 4.40 5.05	1.25 2.30 1.51 2.41
6	17	5' 6"	166	150	60	51	4	0	1+	6.71 6.71 6.81 6.76	4.83 4.72 5.17 5.16	1.88 1.97 2.72 1.52
7	22	5' 2½"	127	121	50½	62½	14	0	8+	5.67 5.51 6.01 6.01	4.60 5.27 4.50 4.93	2.63 2.02 1.07 1.73

* Weight prior to illness.

† Before treatment, edema absent.

‡ Before treatment, edema present.

§ After treatment, edema absent.

|| After treatment, edema present.

On examination, the systolic blood pressure was 72 and the diastolic 48 mm. of mercury. Physical examination gave negative results except for the marked cachexia. The patient was able to be up and about and was reasonably active. The value for serum protein was 7.2 gm. per 100 c.c. She was not anemic. This patient did not remain for treatment.

Comment.—It is of particular interest to note that this patient had never exhibited edema nor was she edematous at the time of examination. Had this patient remained for treatment, she probably would have had edema and a secondary anemia during treatment and the edema probably would have been associated with a fall in the value for serum protein. We agree with Bruckner and his associates that the normal concentration for serum protein had been maintained only in proportion to the blood volume. The dehydration which undoubtedly was present was a manifestation of the disturbance in water balance which had resulted from starvation. Sustaining evidence for these statements will be given later in this presentation.

The emaciation exhibited by this patient (fig. 121a, b and c) together with the emaciation of the second patient at the time she weighed 51 pounds (23.1 kg.) represents the greatest degree of cachexia that we have seen. These weights are comparable with the lowest weights reported and probably represent a complete absence of mobilizable body fat as well as being within a few pounds of the lowest body weight obtainable.

Case 2. Disappearance of Edema and Loss of 9 Pounds Resulting from Dehydration; Gain of 12 Pounds on Replacement of Body Fluids without Reappearance of Edema; Progressive Decrease in Value for Serum Protein.—On November 2, 1941, a girl thirteen years of age was brought to the clinic by her parents because of loss in weight and a change in personality. In March, 1941, she had weighed 114 pounds (51.7 kg.). Schoolmates had ridiculed her because of her weight. She had menstruated normally in April and never menstruated again. Psychosomatic reactions typical of anorexia nervosa had resulted in a reduction in her weight to 66 pounds (29.9 kg.). With the exception of emaciation and hairiness of the arms and legs, physical examination revealed nothing abnormal. No edema was present. The value for serum protein was 6.4 gm. per 100 c.c. The diagnosis was anorexia nervosa.

From November, 1941 to July 18, 1946, the patient was seen at the clinic on three different occasions. Each time she had remained for several weeks during which, as a result of a gradual increase in the caloric value of a high-protein diet, she had reached a diet valued at 3,200 calories. Each visit had resulted in substantial gains in weight but relapses occurred.

On July 18, 1946, at the time of her last admission, she was eighteen years of age, 5 feet, 3½ inches (161.3 cm.) in height and weighed 59 pounds (26.8 kg.) without clothing (fig. 125). This weight was 48.3 per cent of the standard weight of 122 pounds (55.3 kg.) for this age and height. She weighed 55 pounds less than she had weighed five years previously. The most recent loss in weight, however, had been 23 pounds in the six months just prior to her last admission. Edema of the legs, grade 2, on a grading basis of 1 to 4, extending almost up to the knees had been present for five weeks. Emaciation was extreme and pallor was marked. She responded well only to direct questioning. The value for blood sugar was 74 mg. per 100 c.c. and that for serum protein 6.2 gm.; the albumin fraction was 4.40 gm. and the globulin 1.77 gm. The basal metabolic rate was -44 per cent. No anemia was present.

The patient was under treatment for twenty-eight days. As is our custom, at the start, she was not hospitalized. Although she co-operated poorly, only 1 pound was lost during the first nine days. Between the ninth and fourteenth days she lost 2 pounds and edema decreased. From the fourteenth to the twentieth days she refused to drink fluids and until the last day weight of 51 pounds (23.1 kg.) with partial clothing.* An increase in weakness had developed which necessitated her using a wheel chair. She entered the hospital on the nineteenth day. The combination of the dehydration and the emaciation gave her an astounding appearance. On the day of her admission to the hospital, it was found that she had become edema free.

* Body weights on graphs include clothing.

During her eight days' stay in the hospital, she received 1 liter of 10 per cent glucose and saline solution daily. In addition, she received from 1,000 to 1,600 c.c. of food through a nasal tube. She was allowed out of bed and was weighed each day. She exhibited no edema of her legs nor of the dependent portions of her body at any time during her stay in the hospital. She died unexpectedly early in the morning of the ninth day. Permission for necropsy was not granted.

The rapid loss in weight before the patient entered the hospital (9 pounds in eleven days) and the subsequent rapid gain in weight (12 pounds in eight days) can be attributed only to rapid shifts in the water content of the body (fig. 126). During the period of dehydration the value for serum protein decreased although the value for serum albumin remained un-



Fig. 125 (case 2) —Patient on last admission weighed 59 pounds

changed. Also, during the eight day period in which 12 pounds of fluid was retained, the values for serum protein and serum albumin decreased. In retrospect, there seems to be no reasonable doubt that this patient was administered an excessive amount of sodium chloride, although retention of fluid was no greater than the amount that had been lost as represented by a comparison of the body weights at the start of treatment and just prior to her death.

Case 3. Simultaneous, Rapid Gain in Weight, Marked Increase in Edema and Decrease in Serum Protein; Forced Feeding for Four Weeks Without Gain in Weight—On March 29, 1939, a woman, twenty years of age, came to the clinic because of amenorrhea which had been present since June, 1938. In 1937 she had weighed 120 pounds (54.4 kg.). At that time she had been complimented on her small waist line and slim build. She felt that 120 pounds was more

than she should weigh and made a definite effort to reduce by decreasing her diet. Unpredictable vomiting had occurred after meals and she had been nervously and emotionally upset.

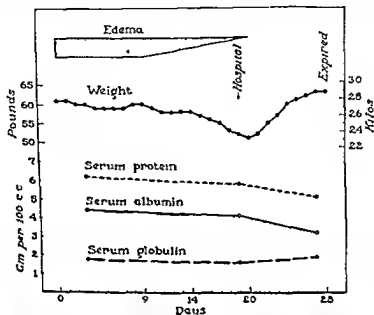


Fig. 126 (case 2) —Edema, weight, serum protein, albumin and globulin for twenty-eight days after treatment was begun. The values for serum protein decreased progressively. Weights shown are with clothing or partial clothing.

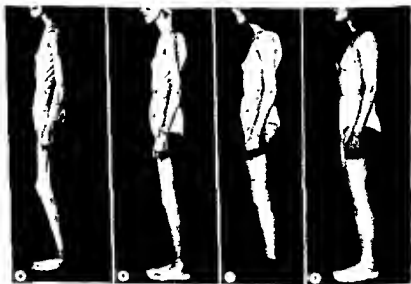


Fig. 127 (case 3) —Patient, a, before treatment, October 25, 1911, weight 61 pounds, b, during retreat of edema November 14, 1911, weight 70 pounds, c and d, after disappearance of edema, c, February 8, 1912, weight 91 pounds, d, June 14, 1912, weight 111 pounds.

At the time of examination she weighed 101 pounds (45.8 kg). The basal metabolic rate was +7 per cent. A diagnosis of anorexia nervosa was made.

The patient returned on October 19, 1911, because of loss of weight and weakness. During

the seven years of her illness she had lost 5½ pounds (2½ kg). She did not eat breakfast and had fruit and coffee for lunch and about the same for her evening meal. Meat was included in her diet as infrequently as once or twice a month. She was especially fond of celery, pickles and lettuce and on occasions would eat several apples each day. Frequently she would have as many as eight cups of coffee a day. She had discovered that eating a little more than a certain amount would cause her to vomit although she never felt nauseated.

On examination the patient weighed 61 pounds (27.7 kg) without clothing (fig. 127a). She was twenty-five years of age and she was 5 feet, 4 inches (162.6 cm) tall. Her weight was 53 per cent of the standard weight of 115 pounds (52.2 kg). There was slight edema of the feet and ankles which had been noted for a period of two months. With the exception of emaciation and hairiness of the arms and legs, physical examination revealed nothing significant. The value for serum protein was 6.4 gm., for serum albumin 4.02 gm. and for serum globulin 2.37 gm. The value for blood sugar was 52.5 mg. per 100 c.c. and the basal metabolic rate was -40 per cent. No anemia was present.

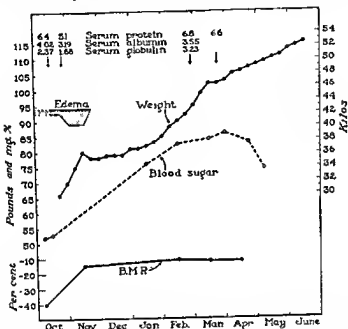


Fig. 128 (case 3).—The plateau in the weight curve following the development of edema should be noted. The value of serum protein decreased with development of edema and the basal metabolic rate increased as a result of treatment. The concentration of blood sugar rose during recovery. Weights are with clothing.

On October 21, 1944, dietary treatment was instituted. The patient co-operated exceptionally well. On the third day edema increased definitely. On the fifth day it was markedly increased and it was impossible for her to wear the shoes she had worn. On the following day there was deep pitting edema of the leg for two thirds the distance to the knee. On the third day a drop in the value for serum protein and a corresponding drop in the value for serum albumin occurred. During the first three weeks of treatment marked increase in edema was present and the patient gained 14 pounds (6.4 kg.; fig. 127b). During the fourth week she lost 2 pounds (0.9 kg.) and the edema decreased. By the end of the fourth week the edema had disappeared and did not recur.

During the second four weeks although the patient co-operated well in taking all of the diet of 3,200 calories, she gained only 1 pound (0.5 kg.). At the end of the eighth week she began to gain steadily and continued to do so until her weight reached 115 pounds (52.2 kg.; fig. 127c and d). This patient required thirty-one weeks to gain 49 pounds (22.2 kg.). Values for serum protein, blood sugar and the basal metabolic rate are given in figure 128.

TABLE 2
GROUP 1: PATIENTS WHO HAD EDEMA AND SHOWED NEGATIVE EFFECTS OF STARVATION, NOT STUDIED IN DETAIL

Case	Age, years	Height	Weight, pounds				Lowest weight, per cent of standard	Edema of lower extremities, grade before and during treatment		Serum proteins, gm. per 100 c.c.		
			Standard	Usual*	Lowest	Loss	Duration of loss, years	Before	During	Total	Albumin	Globulin
8	13	5' 8"	111	107	58	49	11½	1	1+	3.31	3.71	1.77
9	61	5' 4"	141	100	70	59	4	9		3.31	3.12	2.11
10	50	5' 8"	124	110	78	55	2	1	2	3.01	4.13	1.74
11	23	5' 8"	148	128	73	56	3	1	3	3.32		
12	37	5' 8½"	151	150	74	25	19	1	3	3.31	3.43	2.33

* Weight prior to illness.

† After treatment; edema present.

‡ Before treatment; edema present.

§ After treatment; edema absent.

TABLE 3
GROUP 2: ONESE PATIENTS WITH EDEMA WHOSE LOWEST WEIGHT WAS NOT MUCH LESS THAN THE STANDARD WEIGHT

Case	Age, years	Height	Weight, pounds				Lowest weight, per cent of standard	Edema of lower extremities, grade before and during treatment		Serum proteins, gm. per 100 c.c.		
			Standard	Usual*	Lowest	Loss		Before	During	Total	Albumin	Globulin
13	20	5' 8"	132	130	98	32	67.8	2	0	5.4† 2.3‡		
14	24	5' 4"	144	136	115	43	78.4	2		5.0†	2.85	2.06
15	41	5' 5"	145	101	109	63	72.0	0	2	6.20‡	4.65	1.55
16	27	4' 10"	114	175	118	63	68.8	1		6.10†	4.17	2.92
17	20	5' 4"	148	200	119	101	70.8	0	2	5.00‡	4.00	2.00

* Weight prior to illness

† Before treatment, edema present.

‡ After treatment, edema absent.

§ After treatment, edema present.

TABLE 2
GROUP 1: PATIENTS WHO HAD EDEMA AND SHOWED SEVERE EFFECTS OF STARVATION; NOT STUDIED IN DETAIL

Case	Age, years	Height	Weight, pounds				Lowest weight, percent of standard	Edema of lower extremities, grade before and during treatment		Serum proteins, gm. per 100 c.c.		
			Standard	Usual*	Lowest	Low		Before	During	Total	Albumin	Globulin
9	19	5' 9"	115	107	68	45	20.3	1	2+	8.81	3.71	1.77
9	21	5' 4"	144	100	78	50	15.6	2		3.82	3.16	2.11
10	50	5' 9"	141	110	72	54	24.0	1	2	8.22 6.81	1.43	1.74
11	25	5' 2"	112	133	70	56	22.6	1	2	4.51 3.71 3.21 2.81		
12	37	5' 2 1/2"	131	150	72	52	21.6	1	3	6.12 5.61	3.46	2.32

* Weight prior to illness.

† After treatment, edema present.

‡ Before treatment, edema present.

§ After treatment, edema absent.

TABLE 3
GROUP 2: OREXIC PATIENTS WITH EDEMA WHOSE LOWEST WEIGHT WAS NOT MUCH LESS THAN THE STANDARD WEIGHT

Case	Age, years	Height	Weight, pounds					Lowest weight, per cent of standard	Edema of lower extremities, grade before and during treatment		Serum protein, gm. per 100 c.c.		
			Standard	Usual*	Lowest	Loss	Duration of loss, years		Before	During	Total	Albumin	Globulin
13	30	5' 8"	134	150	58	98	3½	67.8	2	0	5.81 6.31		
14	34	5' 4"	144	144	113	45	3	78.4	2		5.01†	4.03	8.08
15	41	5' 3"	145	161	103	88	4	72.0	0	2	6.20‡	4.03	1.33
16	37	4' 10"	114	175	110	65	3½	99.8	1		6.301	4.17	2.54
17	39	5' 4"	145	200	99	101	4	79.8	0	2	6.00§	4.00	2.00

* Weight prior to illness.

† Before treatment, edema present.

‡ After treatment, edema absent.

§ After treatment, edema present.

TABLE 4
GROUP 3. PATIENTS WHO HAD NO EDEMA BUT SHOWED SEVERE EFFECTS OF STARVATION

Case	Age, years	Height	Weight, pounds					Lowest weight, percent of standard	Serum protein, gm per 100 c.c.		
			Standard	Usual*	Lowest	Loss	Duration of loss, years		Total	Albumin	Globulin
18	31	5' 3"	143	90	60	30	5	48.0	5.7 6.5 5.9	8.03 4.54	2.05 1.56
19	44	5' 6"	140	125	60	35	1½	62.0	7.03 6.10 6.50 6.10	8.41 4.60 4.50 3.82	1.03 1.98 1.60 1.27
20	16	5' 3"	114	150	50	50	1	70.1	6.0	4.93	1.63
21	14	5' 4"	123	160	60	41	2	56.0	7.7	4.83	2.77
22	56	5' 6"	123	120	78	41	10	68.5	6.5	4.54	1.91
23	21	5'	118	93	83	10	1	72.1	6.7	1.46	2.23
24	26	5' 8"	148	84	69	16	5	62.5	6.0	1.6	2.1
25	33	5' 3"	137	110	75	37	7	63.2	6.3	4.16	2.03

* Weight prior to illness.

In five cases in group 1 edema was present but the patient did not remain long enough for the curve of gain in weight to be studied. Each patient exhibited definite and severe effects of starvation, as demonstrated by her appearance, mental attitude and the inability to eat more than small amounts of food at any one time. Loss of weight was progressive in each instance at the time of examination (table 2).

GROUP 2

Essential facts are presented in table 3 concerning the five patients in group 2 who exhibited edema as a result of starvation but whose lowest weights were not far below their standard weights although considerable weight had been lost. Two of these patients did not exhibit edema until after dietary treatment was well under way.

GROUP 3

In addition to the eight patients regarding whom the essential facts will be found in table 4 and in the text we have determined the concentration of serum protein of six other patients in group 3. Each of these six patients had lost considerable weight. The weights of these six patients ranged from 83 to 100 pounds (37.6 to 45.4 kg.). They did not show severe effects of starvation. No edema was present and the values for serum protein were well within normal limits.

None of the eight patients regarding whom data are given in table 4 exhibited edema but each showed moderately severe to severe effects of starvation.

COMMENT

From the case reports and the data that accompany them, it is evident that in cases of rapid loss in weight and in cases of marked or extreme emaciation, treatment of the starvation with a diet high in protein and calories is, in some instances, followed in a few days either by the appearance of edema or an increase in any pre-existent edema that may have been present. It is also apparent in other instances in which edema was not clinically recognizable that treatment produced a sufficiently rapid gain in weight to justify the inference that water was being retained by the body in appreciable amounts. Evidence indicative of retention of water may be found in the weight curves, in the appearance of the patient when serial photographs were taken and in some, but not all, cases by a decrease in the concentration of the protein and hemoglobin in the blood. In non-edematous patients, the retained water almost certainly had to be in the extracellular compartments of the body, since the gain in weight was much greater than that which might be accounted for by the formation of new protoplasm.*

Observations of other writers are in keeping with those which we have

* This statement is based on the fact that a rapid gain in weight occurred often when the caloric content of the diet was increased only slightly; for example, from an initial of 800* calories to 1,300 calories, and when there was only a moderate simultaneous increase in the protein content. This gain in weight is often much greater than one could account for, even if nearly all of the ingested nitrogen was retained by the body and none excreted in the urine. The fat and carbohydrate retained as the result of a high-protein diet valued at 1,300 calories would be negligible in weight.

summarized in the preceding paragraph. Keys and his associates in 1946 in studying thirty-four men who volunteered to subsist on a European type of famine diet for six months and who lost an average of 24.5 per cent of their body weight, observed that pitting edema of the legs developed eventually in all but a few of the group. They stated that even in these few exceptions the extracellular space was waterlogged when the thiocyanate method was used. They also found that the development of edema was accompanied by only a small decline in the concentration of plasma protein which averaged 0.73 gm. per 100 c.c. At the same time the ratio of albumin to globulin decreased to only a trivial extent. They found "the ratio of extracellular water to cellular tissue to be roughly double. . . . It is concluded that there is a dynamic nonequilibrium state of the capillary wall and, accordingly, calculations from equilibrium equations are inadmissible."

A number of other pertinent articles in the literature refer to the development of edema which results from a marked increase in the intake of food. McDaniel and his associates in 1946, reporting on malnutrition in repatriated prisoners of war on the U.S.S. *Benevolence*, observed that these patients craved food and would eat several servings in spite of all efforts to prevent their doing so. They reported that 90 per cent of the patients could eat six full meals a day, supplemented by ice cream and chocolate bars, without untoward symptoms. The dietitians estimated that the average repatriate took at least 5,000 calories a day. In this publication one sentence was of particular interest to us: "Some of the patients became edematous after coming aboard." It appears that the authors also observed the development of edema following an increase in consumption of food. In addition, they mentioned that in some cases 24 pounds (10.9 kg.) were gained in as short a time as a week. It is obvious that a large percentage of this gain of 24 pounds in one week must have been due to a retention of fluid, although "the patients on whom this observation was made lost their edema during this time and their well-being increased tremendously." Two of our patients consumed 4,000 calories daily for some time. Although a diet of this caloric value represents a large amount of food, it was consumed long after the expected period for the development of edema and the actual weekly gain in weight, while gratifying, was far less than 24 pounds.

In 1946 Ellis, in reporting his observation on electrocardiographic abnormalities in severe malnutrition present in prisoners of war who had just been released, incidentally observed that in one of the individuals studied, edema of the lower extremities, which had not previously been present, developed after the recovery diet had been followed for seventeen days. This individual had lost about 64 pounds (29 kg.). Edema was present for ten days and then disappeared. No explanation of the edema was attempted. Five days before the edema appeared, the value for plasma albumin was 4.1 gm. and the value for globulin 2.6 gm. At the end of the period during which edema had been present, the value for plasma albumin was 3.5 gm. and the globulin 2.1 gm. These observations in general are in accord with some of the findings we have presented.

Joslin, in discussing the general problem of edema in the diabetic patient paid particular attention to the development of edema resulting from insulin treatment and an increase in the diet. The edema occurring in patients who had not exhibited edema prior to treatment was referred to

as "insulin edema." This edema appeared simultaneously with a rapid gain in weight. It is of interest to note that the development of edema was much more common after the use of insulin than previously and that the greater the degree of emaciation, the more likely the edema was to appear. It appears that the underlying physiologic phenomenon responsible for the development of edema in both the diabetic patient who through the use of insulin had suddenly been confronted with a great increase in available food and the emaciated patient who had anorexia nervosa is one and the same. Our observations throw no light on the theory of edema formation, in fact they were not conducted with that in mind. We are of the opinion, however, that edema and the other consequences of starvation are the result of the same pathophysiologic processes, irrespective of the reason that food is not ingested. Whether a person does not eat because food is not available or whether he refuses to eat because of psychic reasons when adequate food is at hand makes little physiologic difference.

Thus far we have emphasized the waterlogging that occurs in this group of cases. Occasionally, however, one encounters a patient (for example, case 1 and more clearly evidenced by case 2) in whom the disturbance in water balance is manifested by dehydration rather than by waterlogging in the sense that the water of the body has been depleted. This depletion is particularly apparent when the patient not only refuses to eat but also refuses to drink. Such patients exist on an extremely small daily intake of water. The group as a whole drinks far less water each day than the normal individual. Such patients are particularly likely to develop edema when the caloric intake is rapidly increased or when fluids containing sodium chloride are administered intravenously. The practice of administering daily intravenous sodium chloride in routine amounts may be followed by the sudden death of the patient as in case 2.

The plateau in the weight curve has undoubtedly caused confusions and likely accounts for the discrepancies between the caloric intake and the anticipated gain in weight during treatment of anorexia nervosa. These discrepancies not infrequently have been used as evidence to support an otherwise insecure diagnosis of anorexia nervosa, often with the poorly disguised assumption that since the anterior pituitary body can do many mysterious things it also can defy the law of conservation of energy.

SUMMARY

Thirty-one cases of anorexia nervosa have been studied with particular attention to the weight curve during dietary treatment, the occurrence of edema and its relationship to the weight curve and the relationship of the edema to the concentration of the serum protein.

We have deliberately refrained from attempting to support or refute Starling's theory. There is no question, however, that in this group of patients body proteins have been severely depleted. The severity of this depletion is sometimes manifested in the level of the serum proteins and when it is, it implies that the body proteins and also the immediate source of the serum proteins have suffered.

No pitting edema was observed at any time in fifteen patients, while in twelve patients edema was present on admission. Four patients acquired edema during treatment and in six instances pre-existent edema was

increased following treatment. Among the patients who recovered from emaciation and may never have exhibited edema, the character of the weight curve suggested that a sequence of events occurred which was identical in character with those which occurred in patients who did exhibit edema.

In the treatment of anorexia nervosa by the method we have employed, three phases can often be seen in the weight curve. Early in the course of treatment the weight rises rapidly; later it is maintained and a flattened curve results or it may even decrease. In the final phase there is a progressive rise in the weight curve and no edema is present. In the first phase edema may occur or increase if it has been present. In the second phase edema may persist or slowly decrease while the patient gains flesh. The weight of water lost is approximately equal to the weight of the flesh gained. In the third phase the disturbance in water balance has been corrected, waterlogging has been overcome and a progressive gain in weight occurs. The weight curve may be misleading in evaluating the actual storage of flesh.

In severe cases of untreated anorexia nervosa values for the serum proteins more often than not were within the normal range, 6.0 to 8.0 gm. per 100 c.c. In about a third of our cases values lower than normal were encountered. Values of less than 5.0 gm. per 100 c.c. occurred in only one case. The level of the serum protein usually could not be correlated with the presence or absence of edema. With treatment the concentration of serum protein may decrease temporarily possibly because of hemodilution.

The levels of the serum proteins before treatment in the thirty-one cases studied were as follows: from 7.1 to 7.7 gm. per 100 c.c. in four cases; from 6.6 to 7.0 gm. in thirteen cases; from 6.1 to 6.5 gm. in six cases; 5.1 to 6.0 gm. in seven cases and 5.0 gm. or less in one case.

Another incidental but interesting finding was that 16 per cent of the thirty-one patients had a moderate or severe hypochromic anemia prior to treatment and in an additional two patients this type of anemia developed during treatment. The occurrence of edema did not appear to be contingent on the degree of anemia.

FOLIC ACID THERAPY IN NONTROPICAL SPRUE: RESULTS OF TREATMENT IN SEVEN CASES*

JAMES F. WEIR AND MANDRED W. COMFORT

During the latter part of 1945 Spies and his associates reported that synthetic folic acid exerted a favorable influence on the course of macrocytic anemias. Included in their study were cases of tropical sprue in which the favorable response was not only hematologic but also general. The symptoms referable to the alimentary tract in these cases also tended to subside when folic acid was employed. Subsequent reports include those of Darby

* Abridgment of paper published in full in the *Journal of Laboratory and Clinical Medicine*, 32:1231-1241 (Oct.) 1947.

and of Spies and their associates and occasional cases of sprue in papers of other workers who were chiefly concerned with pernicious anemia

Davidson, Girdwood and Innes recently reported results of short periods of treatment with folic acid in ten cases of tropical sprue, idiopathic steatorrhea and celiac disease. They were primarily interested in the hematologic response which they found disappointing. The clinical response was excellent in the cases of tropical sprue and idiopathic steatorrhea but improvement was lacking in the cases of celiac disease. Studies of fat balance were made before and after treatment in seven cases (including one case of celiac disease). In only one case was there improvement in absorption of fat.

Nontropical sprue is a condition characterized by diarrhea, steatorrhea and other gastro-intestinal symptoms, macrocytic anemia, glossitis, nutritional manifestations including loss of weight, weakness, hypocalcemia, osteoporosis, tetany, hypoproteinemia, edema and other changes. These manifestations may vary considerably from case to case. The disease, furthermore, is characterized by a chronic progressive course and often prolonged remissions. Treatment in the past has been based chiefly on the use of a low fat diet and administration of liver extract, calcium and the various vitamins. In general, the results of treatment have been disappointing. In most cases, remission occurred, but the tendency to spontaneous remission has rendered the interpretation of the value of therapeutic agents most difficult.

Stimulated by Spies' earlier reports our group has treated seven patients who had nontropical sprue with synthetic folic acid.* These form the basis for this report. The criteria of nontropical sprue were fulfilled in the opinion of the several consultants who saw the patients. None of the patients had resided in a tropical country.

PLAN OF STUDY

Control data were obtained before institution of treatment. The history included notes about the frequency, duration and severity of the exacerbations and about the severity of the disease between exacerbations, including frequency and character of stools. Hematologic studies included sternal aspiration and examination, determination of the concentration of hemoglobin in grams, erythrocyte, leukocyte and reticulocyte counts and measurement of the erythrocytes with an erythrocytometer. The concentrations of calcium, phosphorus, total protein, albumin and globulin in the serum were determined as well as values for phosphatase and prothrombin times. Roentgenograms of the skull, hands and teeth for osteoporosis and of the small bowel to exclude ileitis and to check for the so-called deficiency pattern, were secured. Roentgenologic examination of the small bowel was not repeated because changes during periods of improvement had not been observed in past experience. In four cases the fecal solids, fat and nitrogen were determined each day during the three-day test period while the patient was receiving a standard test diet of 101.6 gm. of fat, 117.5 gm. of protein, 269.6 gm. of carbohydrate and 2,463 calories. On completion of the preliminary survey a diet containing 50 to 100 gm. of fat, 120 gm. or more of protein and carbohydrate to make the calorie intake 3,000 to 3,500

* The folic acid was kindly supplied by the Lederle Laboratories, Inc.

TABULATION
HEMATOLOGIC DATA IN SEVERAL CASES

Case	Duration of treatment	Folic acid, mg.	Hemoglobin, gm. per 100 c.c.	Erythrocytes, millions per cu. mm.	Morphology of erythrocytes	Erythrocytometer, microns	Reticulocytes, per cent of erythrocytes	Sternal marrow
1	Before		12.3	4.30	Macrocytosis		1	Normoblastic
	1 mo.	50	11.6	3.37	Macrocytosis	8.1-8.3	3.3	Normoblastic
	5 mo.	50	11.2	4.00	Macrocytosis	8.0-8.4		Normoblastic
	9 mo.	50	9.6	3.58	Macrocytosis	8.0		Hyperplastic normoblastic
2	Before		7.6	3.61	Normocytic hypochromic erythrocytes	7.4	1.7	
	1 mo.	50	8.25	3.61		7.6	3.0	
	9 mo.	15	6.4	4.01	Normocytic hypochromic erythrocytes	7.4		
	Before		12.7	4.30	Macrocytosis	7.8-8.0	1.1-2.2	Normoblastic
3	0 wk.	15-190	15.8	4.12	Macrocytosis	7.0-8.1	2.4	Normoblastic
	Before		10.8	3.00	Macrocytosis		0.4-1.0	Megaloblastic
	6 wk.	50	12.0	3.80	Macrocytosis	8.5-7.8	4.9	Normoblastic

5	Before		11 9	3 03	Macrocytosis	8 3		Macronormo- blastic
	2 mo	50	10 8	3 04	Macrocytosis	8 2	3 0	
	5 mo	50	10 8	4 03	Macrocytosis	8 2		
	7 mo	50	9 4	3 30	Macrocytosis	8 2	1 0	
6	Before		10 5	1 23	Macrocytosis	8 0		Normoblastic
	2 mo	50	10 5	4 29	Macrocytosis	8 5		
7	Before		11 0	5 26	Macrocytosis			Normoblastic
	12 mo	15	9 8	4 00	Borderline macrocytosis		1 8	

was used. Vitamins including sufficient vitamin K to control hypoprothrombinemia were given. The dosage of folic acid usually was 50 mg. daily by the intramuscular route. One patient received 180 mg. daily intramuscularly for two weeks while another received only 15 mg. by mouth from the start. Hematologic and chemical determinations on the blood were made each week, the reticulocyte count every other day.

Five of the seven patients were kept under observation at the clinic for four weeks or longer. On dismissal from the clinic the patients continued to take folic acid intramuscularly or orally, the usual vitamins, and, in most cases, calcium lactate in doses of 1 dram (3.9 gm.) three times daily. Some also subsequently were given liver extract. All were urged to use a high carbohydrate, high protein, low fat diet. The dosage of folic acid is indicated in the tabulation.

Some of the patients subsequently returned for observation and hematologic and chemical studies on the blood. In two cases the losses of fecal solids, fat and nitrogen were determined after eight and twelve months of treatment with folic acid. In two cases the fecal components could not be determined because of refusal of the patient or because of his condition.

Each subject on his return home was requested to keep a diary in which was recorded the number of stools passed daily, as well as other manifestations of the disease.

Most important in the discussion of these cases is a consideration of the general status of the patients' health. Only two patients have shown any significant gain in weight or improvement in strength or sense of well-being. One patient had had symptoms of nontropical sprue and diabetes mellitus for three years. No diarrhea was present on admission although the stools contained excess fat. Before treatment with folic acid was started she had gained 10 pounds and further gain was accomplished after this treatment was instituted. This gain was considered to be due largely to an increased intake of food and control of the diabetes as the sprue was in remission at the time of her admission. At the time of dismissal the patient was taking 15 mg. of folic acid daily by mouth and progressed well for three months. Then an exacerbation of the sprue syndrome resulted in her death. The other patient showed definite improvement but it is not possible to state the chief factor responsible for this.

One patient who gave a three-year history of sprue continued to take 50 mg. of folic acid daily intramuscularly at home for one month. At the end of this time an exacerbation of the disease caused him to return to our care. He was in a critical condition as evidenced by dehydration, acidosis and azotemia. In spite of continuation of treatment with folic acid as well as other therapeutic management for six months his general condition did not improve nor intestinal manifestations decrease.

Another patient who had had indications of sprue for seventeen years continued to have exacerbations with varying degrees of edema and tetany and once he had a peculiar paralysis while taking 15 mg. of folic acid daily by mouth. This patient has required frequent hospital admissions during the subsequent eight months.

The patient in one case, while taking 50 mg. of folic acid daily for six months, has had an episode of hypoprothrombinemia (not uncommon in nontropical sprue) with hemorrhagic manifestations and a subsequent acute

exacerbation of the intestinal symptoms of the disease. Two patients did not improve during nine and two months, respectively.

In general, the diarrhea and steatorrhea present before treatment with folic acid have continued during treatment, often with severe flare-ups and there has been no gain in weight, strength or sense of well-being that could not be attributed to remissions in the disease and improved intake of food. The levels of calcium or protein in the blood and manifestations of tetany or edema, when present, have not been improved permanently in any case, even with improved intake of food or other procedures.

Some anemia was present in all cases at time of admission but the value for hemoglobin was 10 gm or more in all but one. The lowest erythrocyte count was 3,030,000. No significant changes in blood counts were obtained from treatment with folic acid. Details are given in the tabulation. General macrocytosis was present in all cases except one, and this patient had the most marked anemia. The macrocytosis persisted after treatment with folic acid in each of the five cases in which re-examination has been done. No change in the erythrocytometer reading was encountered except in one case. In this case the size of the erythrocytes decreased somewhat coincident with a change in the sternal marrow from megaloblastic to normoblastic type. The highest reticulocyte count after commencement of treatment with folic acid was 4.9 per cent on the fifth day of treatment. In general there was little change in the reticulocyte count. However, the degree of anemia on admission was not such that a great response would be expected. In one case megaloblastic bone marrow present before treatment became normoblastic after treatment. In four other cases the sternal marrow was normoblastic before treatment was started. Some of these patients undoubtedly had taken liver extract at varying times before the observations at the clinic. In general, and in spite of this, the hematologic response in this group of cases has been disappointing; the anemia has not improved and the macrocytosis has persisted.

SUMMARY

The following statements seem justified from our observation in this group of seven cases of nontropical sprue. Treatment with folic acid has not resulted in improvement in the sense of well-being or gain in weight or strength that could not be accounted for by increased intake of food and natural remission of the disease. The frequency or severity of the exacerbations of the intestinal manifestations of the disease has not changed. The hematologic response has been disappointing, for anemia and macrocytosis have persisted. All this is in contrast to the favorable results reported in the literature regarding response of tropical sprue to treatment with folic acid. Whether the two conditions are different or the condition in our cases had advanced to an irreversible stage and become resistant to treatment with folic acid is impossible to state. These results indicate that in some cases at least nontropical sprue does not respond favorably to treatment with folic acid.

OBESITY*

CLIFFORD F. GASTINEAU AND EDWARD H. RYNEARSON[†]

Although the dangers and handicaps imposed by obesity have been enumerated by many writers, the seriousness of this disease is not fully appreciated. It is easy to shrug off "a few pounds of overweight" as something of little consequence, but in doing so the physician is ignoring what is perhaps his best chance to lengthen the life and diminish future illnesses of his patient. Statisticians have pointed out the increase in deaths from the degenerative diseases such as cancer, diabetes and heart disease, and the implication has been that medicine is approaching a point of diminishing returns, that increasing efforts will reduce the death and illness rates only slightly. Actually, a great improvement in the health of the nation appears possible by means of the correction and prevention of obesity. Statistical studies have demonstrated the association of obesity with hypertension, pulmonary emphysema, diabetes, heart disease, cancer, acute and chronic nephritis, cirrhosis, accidents and atherosclerosis.

These studies suggest that by the treatment of obesity the physician may ameliorate considerably the effects of many diseases for which otherwise he has little specific treatment. The increased dangers of surgical treatment and pregnancy in the presence of obesity, the greater severity of degenerative arthritis in the knees, hips and lumbar spine of the obese, the increased incidence of gallbladder disease and the earlier appearance of varicose veins are further reasons for the correction of obesity.

A statement which may impress the doubtful patient with the urgency for weight reduction is: "Between the ages of 45 and 55, 25 pounds of excess weight means a 25% greater chance of dying within the next year; 50 pounds of overweight means that you have a 50% greater chance of death in the next year than the person of normal weight."

While there is no question but that obesity increases the incidence of a large number of pathologic processes, it cannot be assumed with such certainty that the reduction of the weight of an obese person to normal will give him health equivalent to that of the person who has never been obese. Some of the changes caused by obesity, such as emphysema, tend to become irreversible in time, but others may be corrected by weight reduction. It seems reasonable to assume that the shorter the duration and the less the degree of the obesity, the more easily will normal health expectancy be restored. It is, therefore, as important to prevent as to correct obesity.

Aside from the reasons mentioned, there are serious psychologic problems stemming from obesity. Marked obesity is essentially a repulsive disease, and its victim tends to feel rejected, unable to join with others in many of the ordinary activities with complete acceptance. Because physical activity requires greater effort for the obese, the victim is likely to retreat to a state of inactivity and thereby perpetuate and accentuate the condition. The frequent occurrence of neuroses in the obese has been emphasized by several investigators. It should be pointed out, however, that similar psychologic investigations of control groups of nonobese persons might have

* From the *Annals of Internal Medicine* 27: 852-857 (Dec.) 1917.

revealed a similar incidence and variety of neuroses. It is of course difficult to judge, also, what proportion of psychologic changes is the result of and how much is the cause for the obesity. Esthetic reasons for the treatment of obesity are not the least important. The desire to be attractive is possibly the most frequent reason that the overweight person goes to the physician for help in reduction of weight.

In consideration of all these factors, it would seem desirable that more doctors develop something of the missionary spirit and zeal in correcting obesity.

PHYSIOLOGY

Early in the investigations of obesity, several cases were reported in which there appeared to be a maintenance of obesity in spite of low caloric intakes. These findings seemed to confirm the popular idea that there are fat people who stay fat no matter how little they eat. However, in more recent and better controlled studies it has been shown that obese persons must eat more than the average person in order to remain obese. This statement has been made previously in many forms and for emphasis it is here repeated: *Fat comes only from food, and obesity results only from eating more than is required to meet the energy requirements of the body.* There are many capable investigators, however, who believe that there are those with a tendency toward leanness who can overeat with impunity, and there are those with a predisposition to obesity who will become stout although eating no greater amount. It is felt by these investigators that some obese persons have an unusual mechanism for conserving energy not possessed by other people. It is sufficient to say that such a mechanism has never been adequately demonstrated, and the very multiplicity of suggested abnormalities of metabolism argues against such a possibility.

There are a number of devices which appear to regulate body weight. Perhaps the most important is the appetite mechanism. No one has been able to explain satisfactorily what determines satiation, but it probably depends upon the interaction of a number of factors. The striking effect of hypothalamic damage in producing obesity through increased appetite suggests that an important center for normal appetite regulation may reside there. The importance of psychic conflict in the development of obesity in persons exhibiting compulsive eating has frequently been observed, thus demonstrating that the cerebral cortex may override the more automatic and primitive appetite control centers.

It is the familiar plaint of the fat person that "I don't eat a thing and I still get fat." It has been well proved that such a person does eat excessively, and it is interesting to speculate why this belief should so frequently arise. A possible explanation is that the person with the predisposition to obesity has an appetite mechanism (whatever that may consist of) which requires a larger than normal amount of food before satiation is accomplished. If he eats what would satisfy the normal person he remains hungry and feels that he has eaten very little; if he eats anything less than what is required for satiation he is likely to believe honestly that he has eaten little, even though he has consumed large quantities of food. A corresponding situation appears to exist for the person with a tendency toward leanness.

Another device for regulation of body weight is the association of energy requirement with the surface area. It has been shown that the number of

calories required by the body at resting state is proportional to the surface area. Thus a thirty-five year old man, 5 feet and 7 inches (170 cm.) tall with a surface area of 1.79 square meters will maintain a normal weight of 150 pounds (68 kg.) with an intake of 2,415 calories each twenty-four hours (tabulation). If he consumes 3,255 calories (34 per cent more) he will gradually gain in weight until he reaches 300 pounds (136 kg.) and a surface area of 2.4 square meters (34 per cent greater). The weight gain of such a man weighing 150 pounds and eating 3,255 calories will at first be 1.7 pounds (0.8 kg.) per week. The rate of gain will gradually become slower until it ceases at 300 pounds. Similarly if this same man weighed 300 pounds and were fed 2,415 calories daily he would lose 1.7 pounds a week at first, the rate of loss gradually slowing as his weight approached 150 pounds. From these figures* it can be seen that a small daily excess of food does not

TABULATION

VARYING FOOD REQUIREMENTS FOR A THIRTY-FIVE YEAR
OLD MAN AT DIFFERENT BODY WEIGHTS*

Weight, pounds	Surface area, square meters	Calories required per twenty-four hours	
		At basal conditions	With moderate activity†
100	1.50	1,560	2,040
150	1.79	1,610	2,415
200	2.02	1,810	2,760
250	2.22	2,020	3,030
300	2.40	2,170	3,255

* These calculations assume a basal metabolic rate of 6 and were obtained by use of the Boothby-Jackson nomogram for a thirty-five year old man 5 feet and 7 inches tall who had a standard weight of 150 pounds.

† Calorie requirements at moderate activity are assumed to be 50 per cent greater than those at basal conditions.

lead to unlimited gains in weight as once postulated by von Noorden, but rather to definite, calculable and limited increases. This removes some of the mystery with which the appetite mechanism was surrounded when von Noorden pictured it as a device of almost incredible accuracy. It also diminishes the necessity for postulating obscure aberrations in energy metabolism which would adjust energy output to fit the intake.

Another phenomenon which aids in the regulating of weight is the fall in the basal metabolic rate with decreased intake of food. After several weeks on a reduced diet, there is often, but not invariably a decrease in the basal metabolic rate. This phenomenon is less pronounced in the obese (as if there were less necessity for conserving their stores of fat) but amounts to

* Calculations were made by means of the Boothby-Jackson nomogram and the factor for predicting weight loss given by Wüster.

lower nervous centers. As the individual matures, the cortex also assumes a greater control over such basic functions as eating, sleeping and procreation. There can be no argument but that our civilization has modified all such functions tremendously, and the aspect that each presents in various cultures is chiefly a mirror of that culture. Eating has acquired a considerable social significance in our own social order, not only in the nature and time of meals but in the amount eaten.

While it is true that most infants and children have less modification of their hypothalamic impulses by the cerebral cortex than do adults, yet Bruch has shown in a series of fundamental articles that obesity of psychologic origin can begin early in childhood. The mothers of such children would go to extremes in protecting their children from even the minor conflicts of living but paradoxically would entertain great ambitions for them. These children would be prevented from playing with other children and would be bathed and dressed by their mothers far beyond the usual age for such care. Within families containing obese children there is frequently a great emphasis on food. Desserts and candies are used as rewards for good behavior; conversation centers around delicacies of the table; and the child gains the feeling that food is the end and purpose of life. The mothers of obese children were found by Bruch to be starved emotionally, disappointed in their husbands, worried over domestic strife and often disappointed in the sex of their children. As if in compensation these mothers attempt to pour out a love to their children that they do not honestly feel. In such an attempt they give the most obvious things, food, protection from the unpleasantness of work and contact with other children "who might play rough"; still these mothers are unable to give their children true affection. Similar situations undoubtedly occur in the lives of the lean however.

Such a situation acting upon a child can lead to obesity in a number of ways. The protection from rough play and exertion diminishes the amount of energy expended. The atmosphere of gormandizing and the continual urging to eat will increase the amount of food eaten. Furthermore, the emotional starvation of the child who perceives the real emptiness of his mother's show of affection may lead to a compensatory increase in food consumption as though the child were trying to satisfy his emotional hunger by the eating of food.

While these factors have been repeatedly demonstrated by several observers, it may properly be asked whether similar factors do not frequently occur without the development of obesity. This view finds some confirmation in the investigations in the etiology of anorexia nervosa. Here is a syndrome, almost invariably a manifestation of an emotional conflict, which has many close similarities to obesity while superficially completely different. Both are disorders of the mechanism which regulates the quantity of food intake. Frequently anorexia nervosa is preceded by obesity or the two conditions may alternate. Both are more frequent in women than in men and both respond most dramatically to proper diet and psychotherapy. This response to diet and psychologic treatment alone is dramatic when contrasted with the numerous articles urging the use of endocrine substances and giving support to endocrinologic theories of causation of the two conditions.

The emotional factors which led to obesity initially should not cause the physician to overlook the conflicts which result from obesity and tend to perpetuate it. The obesity itself becomes a handicap which prevents the patient from obtaining exercise. This in turn diminishes energy output and causes further weight gain. The obesity is sometimes unconsciously used by the patient as a means of protection against doing unpleasant things. Obesity may repel suitors and protect the obese girl from the responsibilities of marriage. It may play a part in the selection of an occupation, preventing the obese person from doing difficult work. The feeling of being set apart from other people because of the physical disfigurement of obesity tends to cause a certain amount of emotional starvation which perpetuates the increased appetite. Not only must the physician overcome the factors which initiated the weight gain but he must solve those which have arisen as a result of the obesity.

Endocrine Factors.—One of the most regrettable practices in medicine is the attempt to diagnose numerous endocrinologic aberrations by means of slight variations in distribution of body fat. These elaborate classifications into types have little or no basis in controlled investigation and are usually misleading.

Pituitary Body.—No definite pituitary obesity has been proved. Cushing's disease now seems to be associated more closely with the adrenal cortex. The posterior lobe of the pituitary has been implicated because some have expressed the belief that an excess of the antidiuretic hormone may cause obesity by retention of water. We are acquainted with no experimental studies which have produced obesity in animals or human beings by the injection of pituitrin, a simple proof if this theory had any basis in fact. Recent experiments have suggested that the pituitary gland may regulate fat deposition through the lactogenic hormone. This awaits confirmation.

Thyroid Gland.—In myxedema and hypothyroidism without myxedema, there is no increased incidence of obesity.

Adrenal Glands.—Hyperfunction of the adrenal cortex may result in Cushing's syndrome. In this condition there is frequently an increase in the total amount and always a characteristic distribution of the adipose tissue. Restriction of diet in Cushing's syndrome will cause loss of weight as in any other obese person.

Pancreas.—True hyperinsulinism (that due to a functioning islet cell tumor) appears to cause obesity by means of an increased appetite which depends upon pronounced hypoglycemia. It has been shown in animals that increased appetite results during insulin therapy only if the hypoglycemia approaches shock levels. Obesity is mentioned as a symptom of the functional hypoglycemia described by Rennie and Howard, but not of that reported by Alexander and Portis. In well-developed obesity, hyperglycemia rather than hypoglycemia is considered characteristic. Therefore it seems probable that hypoglycemia plays an unimportant part in the production of obesity.

Gonads.—There is no definite proof that the gonads have significant effect upon the amount of fat in man, although they may influence its distribution. This contrasts with the effect in animals in which castration is frequently used as a means of increasing the deposition of fat.

Pineal Body.—The evidence is inconclusive that the pineal body has any influence on fat deposition.

Genetic Factors.—The Laurence-Moon-Biedl syndrome consists of mental deficiency, retinitis pigmentosa, hypogenitalism, obesity and polydactyly and appears to be inherited in a recessive manner. The Morgagni-Stewart-Morel syndrome is perhaps better called "hyp rostosis frontalis interna" and is inherited in a dominant manner. It is manifested almost invariably by internal hyperostosis of the frontal bone and headache, frequently by obesity, impotence, amenorrhea, benign hypertensive cardiovascular disease, hirsutism, psychosis of indefinite nature or psychoneurosis, fatigability and weakness; and sometimes by disturbances in olfaction, Bell's palsy, diplopia and amblyopia. Headache is so constant that this diagnosis should be considered in all patients complaining of cephalalgia. In neither of these disorders is there good evidence of endocrine dysfunction or of a disturbed fat metabolism which might cause obesity.

Gurney found that obesity is much more frequent in some families than in others. Experiments with the yellow mouse have demonstrated a form of obesity which is inherited in a Mendelian manner. However it remains to be demonstrated whether the gene or environment is the more important factor in human obesity. While at present we cannot state definitely the importance of heredity in obesity, we can emphasize to the patient with fat parents that he will respond to treatment in exactly the same way as will a person with parents of normal weight. Such a patient should be told that fat is just as dangerous to him as to anyone else and that the fact that his parents were fat cannot be used as an excuse to avoid the necessary corrective measures.

Constitutional Abnormality of the Adipose Tissue.—An abnormal avidity of the adipose tissue of the person "predestined" to be obese has been postulated and named "lipophilia." No proof of this exists. An entity known as "progressive lipodystrophy" characterized by wasting above the waist and obesity below is poorly understood and the emaciation appears to be the significant pathologic aspect of this condition.

Dercum's disease, or adiposis dolorosa, is a syndrome consisting of tender and painful fat nodules in a patient partly disabled by weakness and psychoneurotic symptoms. It has not been established as an entity and nothing of certainty is known of any cause or pathologic physiology.

Disorders in the Use of Energy. Excessive gastro-intestinal absorption.—This has been disproved in experiments which show that obese and normal persons absorb the same proportion of calories, nitrogen and fat from their diet.

Static Obesity.—Obesity due to inactivity and a diminished output of energy means that the appetite mechanism has failed to adjust the appetite to the energy requirements.

Increased Efficiency of the Obese in Doing Work.—Actually the obese person has a decreased mechanical efficiency and expends extra energy in doing the same amount of work.

Abnormal Respiratory Quotients.—The respiratory quotient and its vagaries have been intensely studied for clues to the cause of obesity but no significant deviations have been found.

Reduced Specific Dynamic Action.—This abnormality has not been

demonstrated in obesity when the specific dynamic action is calculated properly

Negative Phase of Metabolism.—Bernhardt thought he had discovered a lowering of the metabolic rate to less than the basal rate after exercise or eating which was peculiar to the obese and effected an economy of energy which explained the development of obesity. This hypothesis was disproved by Wilder.

Luxury Consumption.—This was a device postulated by Grafe and Graham to explain why the normal person did not get fat. The normal person was thought to undergo an acceleration of metabolism after eating which consumed excess food. An absence of this phenomenon was suggested as an explanation for obesity. This theory was disproved by Wiley and Newburgh.

Ketosis.—Ketosis in fasting obese patients has been studied for clues to the origin of obesity, but no consistent abnormalities have been found.

Water Retention.—Water retention has been suggested as a primary cause of obesity. In the absence of pitting edema it is doubtful whether any large accumulation of weight could take place from water retention alone.

TREATMENT

There are no absolute contraindications to reduction of weight. A number of conditions in which reduction had best be done slowly and perhaps only when the patient is grossly obese are active or recently active tuberculosis, active peptic ulcer, gout, cirrhosis, Addison's disease and chronic ulcerative colitis. All of these conditions, except gout and peptic ulcer tend to cause loss of weight so that the incidence of obesity in patients who have such diseases is low. It should be remembered that a properly devised reduction diet is often more nearly ideal for the therapy of the patient's condition than is the diet which is unrestricted in calories and which is selected by the patient himself after a few general directions given by the doctor.

One should be particularly certain that all essential foods are present in diets of children and pregnant women. Old age, hypertension and coronary artery disease are certainly no bars to reduction but rather are urgent reasons for it.

Diet.—This is the most important measure in weight reduction. There is fairly good agreement that a reduction diet should contain an adequate supply of protein (1 gm. or more for each kilogram of body weight), a minimum of fat and enough carbohydrate to prevent wasting of protein. Such a diet permits the loss of large quantities of adipose tissue with little or no wasting of the protein structures of the body. Multiple vitamin supplements are advisable. It is advisable to add sufficient skimmed milk to the diet so that the patient does not require added calcium which, in the forms ordinarily prescribed, are poorly absorbed. The caloric content of the diet should be low enough to insure a definite weight loss and high enough to permit the inclusion of essential food materials. Such diets will provide a range between 600 and 1,500 calories and the selection of the diet should depend upon the physician's estimate of the situation. Space prevents publication of diet lists in this article, but representative diets

may be found in the following references and in a monograph by Rynearson and Gastineau now in press.

It is encouraging to the patient to be told that he will lose a definite amount each week. This can be calculated in the following manner:

1. Determine the calorie requirement for twenty-four hours at basal conditions by means of the Boothby-Berkson nomogram, which is available in Wilder's primer for diabetics. Use the patient's actual height and assume a weight 30 pounds less than his actual weight in employing the nomogram.

2. Add 50 per cent.

3. Subtract the calorie value of the reduction diet selected.

4. Multiply by 0.002. The result obtained is the weight in pounds which will be lost in one week.

Psychotherapy.—Under this term can be placed the impression the personality and attitudes of the physician make upon the patient. Under this term can also be included all of those nebulous psychologic factors that make up the doctor-patient relationship. The physician who by his manner inspires confidence and a desire to follow his orders is most likely to succeed.

Ross has shown quite well how the physician completely convinced of the efficacy of a certain treatment will by his manner transmit that conviction to the patient. If there is a large psychologic element in the illness concerned, then a remarkable improvement follows and the physician is further impressed by the worth of his therapy. A similar phenomenon may occur in the treatment of obesity. The doctor who believes he has found an endocrine or other type of preparation that will cure obesity will have the patient return to his office at frequent intervals for injections. The patient, impressed by the doctor's enthusiasm for his drug, becomes hopeful for success and anxious to aid in every way possible. Under such circumstances it is not surprising that the diet instructions are followed more closely and a good result is obtained. Thus the physician is further convinced of the efficacy of his drug. It is only when the doubting physician uses the drug that it fails.

A disadvantage to the use of any medication is that the patient may decide that the medication is the important factor in therapy and that a few violations of the diet will be of no consequence. Therefore we feel that it is best in most instances to tell the patient that his fat comes from eating too much and that reduction of the amount of food is the only way to reduce his excess weight. Most patients appreciate the honesty of this approach and will co-operate.

Superficial psychotherapy in the form of encouragement and reassurance may be sufficient in the majority of cases, but often the internist will find himself listening to the story of a profound neurosis and occasionally may be forced to refer such a patient to a trained psychiatrist.

Drugs.—Thyroid speeds the metabolism, causes a negative nitrogen balance, exerts a direct toxic action on the heart and has long been used for the treatment of obesity. It is probable that small doses (1 to 2 grains [0.065 to 0.13 gm.] daily) of thyroid are inactivated; larger doses may cause undesirable loss of body protein and an increased strain on a cardiovascular system already overburdened with an obesity-accelerated metabolism.

For these reasons it seems unreasonable to urge the use of thyroid, although many physicians find its use to be without harm when the patient

is followed carefully and occasional determinations of the basal metabolic rate are made.

Other endocrine preparations have been used without effect in obesity. A few of these have been posterior and anterior pituitary extracts, ovarian extracts and estrogens.

Amphetaminic and other sympathomimetic amines have been used as metabolic stimulants and as depressors of the appetite mechanism. It is probable that sufficiently large doses will cause a true depression of the appetite, but it is also likely that an elevation in basal metabolic rate and blood pressure lasting for several hours will follow. Because this effect probably will not be detected if the basal metabolic rate is determined in the morning twelve or fifteen hours after the last administration of the drug, many authors report that amphetamine has no effect on basal metabolic rate.

These amines share with all other medications the fault that they divert the patient's attention from the diet, the most important factor. The use of amphetamine in obesity, within such limits as may be necessary to produce a reduction of appetite of the individual, has been approved by the Council on Pharmacy and Chemistry of the American Medical Association.

In all fairness it should be added that many physicians are more enthusiastic regarding the use of these drugs than are we and they may be correct. More controlled observations are necessary before conclusions are reached.

Dinitrophenol is ineffective without diet limitation and its toxic reactions have caused its use to be stopped.

Belladonna has been used but the results are not conclusive.

Diuretics may give the physician and patient a false sense of achievement by causing the excretion of a few pounds of water.

Salt Restriction and Heat Treatments Which Encourage Perspiration.—These are effective in much the same manner as diuretics. They are of no real value, all weight loss by their agency representing only water.

Exercise and Massage.—These have no effect on local deposits of fat. Exercise is a relatively ineffective means of using energy and vigorous exercise is not wise in most obese patients.

Surgical Measures.—Procedures by which large amounts of fat have been removed have not proved practical.

SUMMARY

Obesity is one of the most pressing and dangerous health problems we face today. Much can be accomplished to improve the health of the general population by a vigorous effort to encourage the obese to reduce.

The development of obesity seems most frequently to depend upon a derangement of the appetite control mechanism. Circumstantial evidence suggests that this mechanism may reside within the hypothalamus and that its functions may be considerably modified by the cerebral cortex. Obesity may result from the inheritance of an appetite control center which demands more food for satiation. On the other hand, the important factor of environment cannot be ignored. Cerebral cortical function in the form of neuroses may modify the more automatic appetite control mechanisms.

A few unusual forms of obesity are recognized. The postencephalitic

specimens. It becomes necessary, therefore, for him to keep familiar with certain diseases of the skin, especially those of neoplastic or granulomatous nature.

THE MODERN SURGICAL PATHOLOGIST

In the practice of modern surgical pathology the pathologist, in order to render efficient service to the patient and the surgeon at the time of the operation, must have at his disposal a laboratory equipped to make frozen sections of fresh tissue for microscopic examination. Such a laboratory should be so situated that it is easily accessible to the operating rooms. In hospitals where operations are numerous and various, the pathologist often has to be ready to determine, if possible, while the patient is on the operating table the pathologic nature of tissues removed from different parts of the body. In the microscopic examination of tissues the pathologist has to be very careful and at all times exercise good judgment as his findings not infrequently determine whether a conservative or radical operation is to be performed. If the pathologist is in doubt as to the true nature of a fresh specimen of tissue after making a microscopic examination, it is always best to defer the diagnosis and fix the tissue preparatory to making fixed frozen sections, paraffin sections, or eeloidin sections, according to the choice of the pathologist, for microscopic examination. If after a careful microscopic examination of the fixed tissue sections the pathologist is still unable to decide whether a given specimen is benign or malignant, it is best to call it benign and, if practicable, ask for another specimen. In other words, as far as malignant neoplasia is concerned, it is generally better to make an error of omission than one of commission.

The day is passing when the surgical pathologist can do full justice to the patient by simply making a diagnosis of carcinoma, sarcoma and so forth. The modern surgical pathologist is supposed, if possible, to determine the type of malignant neoplasm with which he is dealing, indicate its numerical microscopic grade of malignancy and, when practicable, to determine to what extent the neoplasm has spread by direct invasion, metastasis or both. It goes without saying that some neoplasms are so undifferentiated and hence highly malignant that it is practically impossible to make a diagnosis other than a malignant neoplasm, grade 4. The numerical microscopic grade of a malignant neoplasm arrived at as the result of the microscopic examination of specimens removed for biopsy or of the whole growth (a carcinoma of the lip, for example) may influence to a considerable degree the therapeutic procedure in a given case. Such influence is especially noticeable in the treatment of carcinomas of the lip, larynx, urinary bladder and rectum. Furthermore, the surgical pathologist, although it is out of his field, now is supposed to know something about the sensitivity to irradiation of various malignant neoplasms.

A surgical pathologist is not infrequently called on at the time of an operation for a malignant neoplasm to determine whether the surgeon's line of incision is beyond the neoplasm. This is very important, as the sole object of a skillfully performed operation would be defeated if a portion of malignant neoplasm that could have been removed if detected at the time of the operation is left in the patient.

When I referred to the encroachment of the work of the surgical pathologist on that in another field, I did not mean the field of postmortem pathology, with which he is closely allied; however, I did mean for the most part although not entirely that branch of clinical pathology known as "mycology." Pathologists throughout the country are more or less familiar with such diseases as actinomycosis, blastomycosis and torulosis, and pathologists, especially in California, are familiar with the disease commonly known as coccidioidal granuloma. However, I should like to call attention to the fact that diseases are cropping up in this country now with which most surgical pathologists are not familiar, despite the fact that some of them at least may be common or fairly common in other parts of the world. I am referring to such diseases as histoplasmosis, toxoplasmosis, mycetoma or Madura foot, rhinosporidiosis and sarcosporidiosis. The surgical pathologist in this country should not be expected to become an expert in the diagnosis of these diseases. He should acquire enough knowledge about them, however, so that he will promptly realize when he encounters one of them that he will need the assistance of someone familiar with such diseases in order to make a correct diagnosis.

EARLY AMBULATION IN POSTOPERATIVE CARE*

EDWARD S. JUDD, Jr.

My personal interest in getting patients up early after major surgical procedures was stimulated during a part-time assignment at a state hospital for the care of insane patients. At that time, throughout the United States, the routine plan of immobilization of the surgical patient for a period which usually lasted at least ten days was very much in vogue. Observation on some of these insane patients at first was very startling. When I made rounds I was surprised to note that patients who had undergone gastric resection or operations of similar magnitude on the previous day were up and about in spite of the very strict orders that they were to remain in bed. The attendants at the institution assured me that they had learned that there was no particular reason for applying restraints to these patients as they all appeared to do equally well whether they were up or not. I soon learned to omit all strict orders for immobilization and was gratified to see how well the patients withstood what appeared to me to be a rather radical program. After noting that there were no deleterious effects, I extended this type of routine in a limited manner to patients in other hospitals. I very quickly adopted it on a wide scale and have been most enthusiastic about it ever since.

My early conclusions appeared to be supported by observations made after operations had been performed on children. The children appeared to react in a satisfactory manner without any particular restraints. In

* Abstract of paper read at the meeting of the Postgraduate Medical Assembly of South Texas, Houston, Texas, December 1 to 3, 1947.

fact, if they are allowed to become ambulatory when they wish, there seems to be an automatic mechanism that gets them out of bed at a very natural time. Certainly, no harmful effects have been noted and there appears to be no logical reason why a similar situation should not prevail with their elders.

REASONS FOR EARLY AMBULATION

In any program as contradictory to the old teachings as early ambulation appears to be, the features might be divided roughly into two great classes—first, the hopes, and second, the fears. The most important of the hopes that surgeons held was that of overcoming the ever-present threat of venous thrombosis and pulmonary embolism. For some time, in the early postoperative care of patients who had undergone major operations, it had been the practice, on some of the surgical services at the Mayo Clinic, to administer thyroid extract several times a day in the hope that it would accelerate the peripheral circulation and maintain the pulse rate at more than 100 beats per minute. The trend toward early ambulation has been motivated by the rationale for the postoperative administration of thyroid, although this agent is seldom used for this purpose at present. It has seemed logical, however, to hope that early ambulation would reduce the incidence of thrombosis and embolism rather sharply. Whether it actually will do so remains to be seen. Evidence at hand suggests that it has not lived up to expectations in this respect.

In the case of elderly patients, all surgeons were familiar with the general deterioration that seemed to occur after the patients had remained in bed for a week or more. The incidence of pneumonia, congestive heart failure, urinary retention, intestinal distention and actual mental disorientation was rather high. It was hoped that many of these complications could be prevented by early ambulation. I believe it is fair to state that this hope has borne fruit and that there has been no more gratifying change in the postoperative state than the decrease in the incidence of these complications.

The fears that might attend the institution of early ambulation are largely associated with the wound itself. It seems entirely illogical to expect an abdominal wound to heal properly if the patient is not immobilized for a long time. These fears have certainly been groundless, and almost all authors are unanimous in admitting that wound disruption has not been increased by the use of early ambulation; in fact, some surgeons have gone so far as to state that the wound appears to heal more satisfactorily. Ingenious theories have been advanced to explain this result, and some of them have been accompanied by what appears to be unquestionable experimental evidence.

USE OF EARLY AMBULATION ON THE AUTHOR'S SERVICE

I have been enthusiastic about early ambulation for several years. My early impressions about this method of treatment were further confirmed by my observation of large numbers of patients in military hospitals, especially in hospitals throughout the Pacific area. Information that I acquired in this manner has been put to good practical use.

In cases in which a major abdominal operation has been performed,

the patients are permitted to get out of bed as soon as they desire to do so. If they experience any difficulty in micturition, they are encouraged to get out of bed on the evening of the day of operation. On the day after operation, they are advised to get out of bed at least for a few minutes.

At first, I employed a gradual program which consisted of having the patients raise themselves gently to a sitting position and then dangle their legs over the edge of the bed. This program later was liberalized and the patients now are permitted to get out of bed immediately. They are not urged to get out of bed until they are willing to do so and until they are certain that early ambulation will not do any harm. Ward patients and patients who share rooms with other patients almost invariably get out of bed much earlier than do patients who are in private rooms. This probably is due to the element of competition. After the patients are up, a fixed routine is not followed. In the average case, the physical activity will be regulated automatically and the patients are permitted to be up as much as they desire.

Although retention sutures are no longer used by some surgeons, they still may be employed to good advantage, especially in the closure of incisions made at the site of previous incisions and in cases in which the patients are obese. In addition, long butterfly tapes are used when indicated and a scultetus binder is used for a few days to give the patients at least a feeling of security.

The impressions that I have gained in the last several years by observing a large number of patients who have been treated in this manner have been the same as those of many other authors. Certainly, there has been a sharp decrease in the incidence of postoperative atelectasis and other pulmonary complications. The degree of ventilation that the patients have been able to effect for themselves has been increased greatly. Gastric and intestinal distention, which formerly was a serious problem, has been much less troublesome. The peristaltic function has returned at an earlier date. The patients have been able to use the bathroom for elimination, which has been an important psychologic factor in their recovery. Much of the constipation and distention which still occurs appears to be attributable to the reluctance of patients to use the bed pan even for a few days after the operation. Gastric retention, which formerly occurred very frequently after operations on the upper part of the abdomen, seldom is observed in cases in which early ambulation is used. The incidence of postoperative urinary infection also has been greatly reduced. This is a rather obvious advantage of early ambulation since the patients are able to empty their bladders and prevent urinary stasis which formerly led to secondary sepsis. The amount of time and effort spared the interns and the nursing staff makes this advantage alone well worth while. One of the most gratifying advantages has been the improvement in the general condition of the patients. Their appetites appear to return much more quickly and to be of a more normal type. The very fact that the surgeons allow them to get up so soon after operation conveys the impression that the surgeon expects them to get well promptly. This improves the patients' morale and influences them to return to their homes at an early date. The economic aspect of such a situation is very obvious and in this day and age it is of tremendous importance.

THROMBOSIS AND EMBOLISM

A study of a large number of cases of postoperative venous thrombosis and pulmonary embolism has proved that definite statements cannot be made regarding the value of early ambulation in reducing the incidence of these complications. It originally was hoped that this form of treatment would cause an appreciable decrease of these serious complications. The effect of early ambulation on these complications apparently has not been as great as surgeons had hoped that it would be. This observation has been confirmed by Ravdin. The fact remains that surgeons who are using early ambulation still are observing thrombosis and embolism.

CONCLUSIONS

In conclusion, I believe it is fair to state that early ambulation as an adjunct to modern postoperative care has withstood the test of time. It has been used by surgeons and investigators working in all fields under all types of conditions, civilian and military, and in all types of hospitals. The early fear, namely, that it would prevent proper healing of the wound has been proved to have been unwarranted. In a large majority of cases, the results of early ambulation have been more promising than those originally expected. The one great disappointment appears to be the failure of this method of treatment to reduce the incidence of thrombosis and embolism. In any event, on my surgical service, early ambulation has proved to be a valuable adjunct and is used routinely.

SURGICAL USES OF POLYTHENE: AN EXPERIMENTAL STUDY*

JOHN H. GRINDLAY AND FRANK C. MANN

Polythene, a polymer of ethylene and a flexible plastic substance, appears to be well tolerated by living tissue.

Extruded polythene tubes of small diameter have been used with great success as cannulae in blood vessels and lymphatics. Blood and lymph do not readily clot in these tubes.

Polythene film has been used to replace surgically excised dura and polythene tubes have been used for ventriculostomy tubes in dogs and monkeys. No undesirable reaction has occurred and no ill effects have been noted during an observation period of one year.

Molded polythene tubes have been used for anastomosis of the normal and obstructed common duct in a series of dogs. During the period of a little more than a year that some tubes have remained in place the dogs have had no signs of obstruction of the common duct and the tubes have shown no signs of becoming occluded.

Molded polythene tubes have been used for anastomosis after resection of a segment of trachea, and for implantation in the normal trachea and

* Abstract of paper published in full in the *Archives of Surgery*. (In press.)

main bronchi, in a series of dogs. No significant local reaction and no retention of secretion caudal to these tubes has been observed, even in dogs that have now had such tubes for one year.

Two-piece molded polythene tubes have been used in a series of dogs for anastomosis after resection of the lower part of the colon. Tubes have been passed, during defecation, in about a week. Leakage at the anastomosis and stricture of the bowel have not occurred.

MEDICAL EDUCATION*

DONALD C BALFOUR

The need for expansion of medical schools and hospitals has been brought about because medicine and medical science have advanced with such bewildering swiftness that this past decade has been one of the most amazing eras that has ever been recorded in medicine. In this short period have come discoveries which have saved millions of lives: the antibiotics, the magic of chemotherapy and of radioactive substances, dramatic advances in vascular surgery and a host of other spectacular achievements in all fields. In this forward march of medicine, one common factor has been obvious, namely, that research and experimentation in the basic medical and physical sciences has been the basis for these advances. The pattern of applied research in medicine has been so generally accepted and so productive that it is not surprising that all great medical centers are embarking on extensive programs in the development of medical research with the primary purpose of integrating this with the better care of the sick.

All of these projects are evidence that medical schools realize they are seriously lacking in the facilities necessary to take advantage of what has been achieved in the recent past, and it is for this reason that the status of medical schools assumes such significance in relation to the general objectives which are being followed in great medical centers throughout the world.

Those who have had an opportunity of visiting Great Britain, Scandinavia and other parts of Europe in recent months have been amazed at the ability of men in medicine to re-establish their research activities quickly, particularly in those centers which held a high place in medical science before the war. In this country ambitious plans are under way in many institutions. This world-wide effort to advance medicine and bring better medical care for the people of all nations constitutes a great challenge to America.

It has become important, because of advances in medicine in recent years, that the medical schools greatly expand their facilities for teaching the art of the practice of medicine and for investigation into the causes and the cure of those conditions which still are not completely understood.

* Abridgment of paper read at the meeting of the Chicago Association of Commerce and Industry, Chicago, Illinois, November 19, 1947.

The real problem confronting medical schools today in meeting their responsibilities is in the great increase in the cost of medical education. Studies made by the American Medical Association have shown that \$43,000,000 will be needed to operate the medical schools of this country in the coming year. Of this sum, students' fees will provide no more than \$12,000,000. The remaining \$31,000,000 will be obtained from income from endowments, general university funds, appropriations from tax funds, gifts and similar sources. The fact that only 28 per cent or less of the total cost of undergraduate medical education next year will be met by students' fees is impressive evidence for the frequently repeated statement that income from tuition provides but a small fraction of the financial support required by medical schools.

TREATMENT OF ALLERGY TO INSULIN WITH DIPHENHYDRAMINE HYDROCHLORIDE: REPORT OF TWO CASES*

MILLO D. LEAVITT AND CLIFFORD F. GASTINEAU

Two cases in which allergy to insulin characterized by generalized urticaria was exhibited have been reported.

Studies conducted reveal that, in these two cases, benadryl (diphenhydramine hydrochloride) favorably modified the dermal symptoms of the allergic state and afforded a satisfactory method for treating such symptoms.

In the light of these results it would seem desirable to have a solution of benadryl available for parenteral administration. Such a solution might be effective in the treatment of localized allergic reactions to a number of injected substances, such as liver extract, hormones, drugs and serums as well as to insulin.

USE OF ANTIHISTAMINIC DRUGS IN TREATING PATIENTS ALLERGIC TO LIVER EXTRACT†

HADDON M. CARRIER AND GILES A. KOELSCH

It is occasionally necessary to administer extracts of liver to patients sensitive to this substance. The essential features in twenty cases in which allergic reactions resulted from the parenteral use of concentrated liver extract were studied. In eight recent cases the combined use of antihistaminic drugs and liver extracts has proved helpful in the solution

* Abstract of paper published in full in the *Archives of Internal Medicine*, 80:271-280 (Aug) 1947.

† Abstract of paper published in full in the *Journal of Allergy*. (In press.)

of this problem. In only two of these eight cases have untoward reactions necessitated the stopping of parenteral administration of liver extract. One was in a patient whose allergic manifestation was that of atopic dermatitis. Pyribenzamine is being successfully used in a similar program.

The other case was of particular interest. This patient tolerated injections of liver for five years and became sensitive coincidently with early manifestations of Addison's disease. Sensitivity to histamine has been definitely shown to be affected by the adrenal cortical function. Adrenalectomy or hypophysectomy, allowing adrenal cortical atrophy, in guinea pigs or in rats will greatly decrease the minimal lethal dose of histamine for those animals. Replacement therapy by extracts of adrenal cortex will allow the natural resistance to histamine which in the rat is high, to assume essentially normal values. With these facts in mind it is apparent that the development of Addison's disease may have contributed to the sensitivity the patient manifested to the injection of liver extract. Bringing the Addison's disease under control likewise may have contributed to his improved tolerance to extracts of liver subsequently administered.

LABORATORY ASPECTS OF CERTAIN TROPICAL DISEASES*

THOMAS B. MAGATH

The world-wide dispersal of members of the American armed forces, and particularly their relation to the tropical zone, has stimulated a great deal of thought and discussion concerning the possibility of the implantation of exotic diseases into the United States. The evidence now available indicates that this threat has not been, and probably will not be realized. However, because several hundred thousand Americans were personally exposed to diseases which are either absent from or rare in this country and because the airplane will increase traffic throughout the world, it is necessary that physicians constantly be on the lookout to detect and treat diseases which are, to a great extent, new to them. Since, for the most part, these diseases can be diagnosed with absolute assurance only by laboratory procedure, it therefore will devolve on clinical pathologists to make the final diagnoses; it is hoped that the anatomic pathologist will rarely be needed.

VIRUS AND RICKETTSIAL DISEASES

A fairly large number of virus and rickettsial diseases were encountered in the armed forces; however, few persons, if any, arrived on these shores still suffering from these diseases. Epidemic typhus was most feared but it is not usually found in the tropics unless at high altitudes. The rarity with which it occurred was highly significant. In the diagnosis of the condition and its related infections, endemic typhus and scrub typhus or tsutsugamushi disease, the laboratory can contribute to the diagnosis by

* From the Texas State Journal of Medicine 44:316-320 (Aug.) 1948.

a test of the ability of the serum to agglutinate certain strains of bacteria of the genus *Proteus*. In epidemic and endemic typhus the serum of the patient frequently agglutinates *Proteus* OX19, while in scrub typhus the serum agglutinates *Proteus* OXK. Weak cross agglutination is sometimes present but the most significant finding is a rising titer during the course of the disease. Because in Rocky Mountain spotted fever and endemic typhus there is usually a positive agglutination test with *Proteus* OX19, one must be on guard to learn whether the patient formerly had one of these diseases as a result of which he still has a positive agglutination test. Marked interstitial myocarditis is always present in scrub typhus when death is due to the disease. Complement fixation has recently been successfully used by Irons, Murphy and Wolfe in the diagnosis of Q. fever, but the test is not easy to perform.

The diagnosis, from a laboratory standpoint, of diseases of virus origin is laborious and requires facilities not usually available. Thus the specific identification of the viruses of psittacosis and yellow fever involve use of specific antigens for complement fixation or animal passage of the virus for diagnosis. Of course at necropsy the characteristic pathologic lesions of the liver are diagnostic of yellow fever.

RELAPSING FEVER

In certain tropical and subtropical countries the occurrence of relapsing fever caused by *Leptospira* is fairly common but the duration is self-limited and the chance of finding the disease in returned personnel is small. In Texas the disease is rather common in certain localities and no doubt the pathologists of this state are familiar enough with methods of diagnosis. The easiest and most direct laboratory examination is by staining a thick smear with Giemsa's stain. The slide should not be fixed, although ordinary thin smears stained by Wright's stain usually reveal the organism. These methods are more reliable than the darkfield method which, in blood examination, is fraught with difficulties due to artefacts which resemble spirochetes. In large series of cases the stained slides reveal more positive findings than does the darkfield method.

MALARIA

By all odds the most important disease which is encountered in persons from the tropics is malaria. It is important to note that with all the agitation and writing relative to this disease in the past few years, there are many physicians and technicians who as yet have no idea what a so-called thick smear means and have never seen one, yet this is the most important diagnostic method available for the detection of infection by plasmodia. It is interesting to note in passing that the thick smear method of diagnosis was devised by Ross in 1895 but was neglected for years until it was used in survey work in the tropics comparatively recently. The method was extensively used for survey and diagnostic work in World War II.

It is true that thin smears stained with Wright's, Giemsa's or any similar stains will reveal plasmodia readily when present in large numbers and even when present in moderate numbers if a long and diligent search is made. As a matter of fact it is frequently necessary to study the parasite

in thin films in order to identify the species. As a rule the thick smear represents a concentration of at least 100 times that in a thin smear, and examination of one hundred and fifty fields, which can be done in three to seven minutes, will furnish an adequate basis for reporting the slide negative if plasmodia are not found.

While the details of the method may be had by consulting the numerous papers on the subject, it is important to note the great stress laid on the matter of cleanliness of the slides and on the facts that several drops of blood should be used and that the area covered by the blood should be not greater than about 1 cm. in diameter. After thorough drying, the slide should be stained in an aqueous solution of stain which will lake the erythrocytes during the staining process. The stain of choice is Giemsa's. A description of the best method of preparation of the solutions may be found in a paper by Roe, Lillie and Wilcox.

All investigators have indicated, in various references, that the most disappointing accident that may happen in use of the thick smear method is the failure of the smear to stick to the slide. They imply that this catastrophe is caused by the use of dirty slides, contact of the slide with the patient's skin or staining before thorough drying. Several methods have been proposed for the actual making of the smear but no one implies that this phase of the procedure is a critical one. Thus, some use a toothpick; others, like Krauss, "with the corner of another slide spread the drops of blood to the size of a one cent piece by describing centrifugal circles." As a matter of fact, this is the critical stage in the process, and unless the blood can be made to adhere to the slide there is no value in the method. It is best to stir the blood well with whatever instrument is used so that the area of the glass under the drop is thoroughly wet with the blood. Krauss' method is excellent for this purpose and, if energetically carried out, will help to throw the infected cells to the periphery to which the search can be limited. Just what factors are involved in causing the blood to stick to the slide are unknown but whatever they are, the process of stirring accomplishes the result.

Rather recently a number of papers have dealt with precipitin and complement fixation tests in which antigens made from plasmodia of animals other than man are used, but at present no such antigen is available for any use other than that for restricted investigative procedures; the thick smear is still the method of choice for routine use in diagnosis.

LEISHMANIASIS

One of the diseases which occurred in limited incidence in our armed forces was leishmaniasis of the cutaneous variety. In typical cases a smear made by scraping the edge of the ulcer will reveal the typical Leishman-Donovan bodies if stained with one of the standard Romanovsky stains. In relatively long-standing cases and in those in which secondary changes due to bacterial invasion have taken place, it is best to resort to a cultural method as outlined by Packhamian.

Sterile meat infusion agar, which contains 1.5 to 2 per cent of agar-agar, is cooled to 45°C. and about 20 per cent of defibrinated rabbit's blood is added, mixed well, poured into test tubes and allowed to solidify in a slanted position. In order to obtain a large amount of water of conden-

sation, that is, about 0.5 c.c. per tube, the freshly prepared tubes of medium are first refrigerated for several hours and then warmed at room temperature. After incubation overnight to assure their sterility, the tubes of medium are stored in the refrigerator until ready for use.

In order to avoid contamination of the cultures with bacteria and molds, the lesions are painted with tincture of iodine and, after removal of the excess of iodine with alcohol, from 1 to 2 c.c. of sterile isotonic solution of sodium chloride is injected into the bordering inflamed zone closely adjacent to the ulcerous center of the lesion. It is desirable to use a newly sterilized needle and syringe for each injection and to introduce the solution into different parts of the inflamed margin. Immediately thereafter a few drops of fluid are obtained by aspiration and each sample of the aspirated fluid is inoculated into separate tubes of the medium. The inoculated tubes are rubber-capped and kept at room temperature (about 25°C.) for about two weeks before they are examined for flagellates.

Smears made from cultures showing a growth of flagellates are fixed with absolute methyl alcohol and stained by MacNeal's tetrachrome or a combination of the Wright-Giemsa methods.

In the search for parasites in kala-azar, the blood of the patient may be cultured by the method just described or smear preparations may be made from the bone marrow or from the spleen after splenic puncture; cultures of aspirated material from the bone marrow or spleen also may be made. One should be on guard in examining smear preparations lest one be confused by the appearance of yeasts in the smears and, more particularly, by the presence of *Histoplasma*. These latter organisms greatly resemble *Leishmania* and many errors have been made by mistaking these two forms.

FILARIASIS

It has been noted by all those who have studied the patients who contracted filariasis during the war that there is little to be gained by further study of the blood of these patients with a view to finding microfilaria. These organisms appeared in small numbers in only a few patients. However, if patients are suspected of having filariasis the only way a positive diagnosis can be made is by finding the adult organisms in a lymph node by biopsy or by finding the microfilaria in the blood. Occasionally a roentgenogram may show a calcified adult organism in a lymphatic plexus. If the infection is a heavy one the organism may be seen in a drop of capillary blood, either stained or unstained. The thick smear technic used in the diagnosis of malaria is satisfactory. If the organism is suspected of being *Wuchereria bancrofti* the blood should be taken after 10:00 p. m. and before 4:00 a. m., if the thick or thin smear method is to be used. The best method of procedure, however, is to use venous blood taken during the daytime according to the following method:

Withdraw 2 c.c. of blood and divide equally into two 15 c.c. centrifuge tubes which contain 1 per cent solution of acetic acid. Immediately shake vigorously; this is the important step in the procedure and if the tubes are not vigorously shaken the erythrocytes will not be completely laked. The tubes are centrifuged at moderate speed for ten minutes, the supernatant liquid is decanted and the sediment is examined under the microscope.

During the past six or seven years a number of papers have appeared relative to the use of skin tests for the diagnosis of filariasis. The antigens have been made from various microfilaria obtained from animals, the most common one being *Dirofilaria immitis* from the dog as described by Saunders, Bianco and Jordan. These antigens have been reported to give a high percentage of positive reactions in persons suffering from filariasis; however, the status of these tests is still obscure. All the general objections, well known with reference to skin tests as diagnostic procedures, apply to the skin test for filaria and, in addition, there is evidence that these species give cross reactions with each other. For example, antigens made from *Dirofilaria immitis* give almost as high an incidence of reactions in persons with onchocerciasis (Bozicevich and associates) as do antigens made from *Onchocerca volvulus*. The very fact that an antigen made from *Dirofilaria immitis* is used to diagnose *Wuchereria bancrofti* should furnish evidence enough that caution is needed in interpreting the results of these tests.

Onchocerciasis can, with certainty, be diagnosed by finding the worms in the tumor, which is readily excised, or by finding them in either fresh slivers of skin removed from the face and pressed out between slides or in stained sections of the skin.

ENDAMOEBIA HISTOLYTICA

One of the most important laboratory diagnoses with relation to tropical diseases as well as to those of the temperate zone, is that of infection with *Endamoeba histolytica*. In spite of the numerous articles which have been published with reference to diagnosis by cultures and complement fixation, direct examination of the stool remains the standard and only practical procedure available.

If the patient is having loose stools, most of the amebas appear in the trophozoite stage; however, if the stools are formed, a dose of Epsom salts will assure that the motile form will appear. The advantage of examining stools after the administration of salts is that it is necessary to examine fewer stools in order to find the Protozoa. Thus, in a large series, after administration of Epsom salts examination of a single stool will yield positive results in about 75 per cent of cases, while examination of three specimens from a patient will yield positive results in upward of 96 per cent. If formed stools are examined, a single stool will yield positive results in about 30 per cent of cases and it will require at least ten stools in order to approach a 90 per cent yield. *Dientamoeba fragilis* is especially difficult to find in formed stools.

Because the cysts are found in formed stools one should use the zinc sulfate flotation method if it is necessary to concentrate the cysts. The technic is as follows.

Prepare a 1 in 5 suspension of formed fecal material and tap water. Filter through four layers of gauze into a 13 by 100 mm. tube until the tube is about half full. The amount of filtrate will be approximately 4 c.c., but the amount needed will depend on the heaviness of the suspension; the sediment after centrifugation should cover the bottom of the tube to a depth of not more than 2 mm.

Fill the tube with tap water to within 6 mm. of the top. Be careful not

to overflow the tube. Invert to mix. Centrifuge one minute at moderately high speed. Pour off the supernatant fluid. Repeat this washing two more times, or until the supernatant fluid is clear. Usually two or three washings are sufficient.

Fill the tube half full with zinc sulfate solution which has a specific gravity of 1.180 (the zinc sulfate solution is made by weighing out 331 gm. of $\text{ZnSO}_4 + 7\text{H}_2\text{O}$ and adding water to make 1,000 c.c. and a specific gravity of 1.180). Agitate to mix, but do not invert. With a pipet add zinc sulfate solution to within 6 mm. of the top of the tube. Do not invert the tube. Centrifuge for thirty seconds.

With a wire loop, bent at right angles, remove 3 or 4 loopfuls from the surface of the liquid and place on a slide. Add one or two drops of 1.5 per cent solution of iodine with potassium iodide, cover with a 22 mm. square no. 2 coverglass and examine under the microscope.

Standard textbooks describe the characteristics of the various cysts and trophozoites of the five amebas of man; however, it should be observed that three species of mature cysts, including *Endamoeba histolytica*, have four daughter cells and that the cyst of *Endamoeba coli*, at one stage in its development, also has four nuclei. It is the morphologic characteristics of the cyst and not the number of nuclei that determines the species.

The examination of amebas in their motile state requires fresh warm stools and skill in detecting small morphologic details. The well-described characteristics of these amebas are not so clear to the observer as to the writer of the text. Frequently resort must be had to slides stained with iron-hematoxylin. These should be fixed in Schaudinn's fluid or, if *Dientamoeba fragilis* is to be differentiated, in Bouin's. The staining method of choice is the so-called loop process with iron-hematoxylin, and its advantages outweigh those of the newly described short processes (Magath).

One must become familiar with the low power of the microscope in searching for amebas. It is necessary to cover large areas on slides in order to find the occasional parasite. This can only be accomplished by using a magnification of 100 diameters. If the examiner attempts to cover the field with a higher magnification, he will find that he will not cover a sufficient area. The higher power is needed to identify the parasite after it is found.

INTESTINAL WORMS

One of the most important examinations of persons who have been in the tropics is that designed to detect intestinal and hepatic worms. It is hardly necessary to point out that the gross examination of the stool may reveal the presence of tapeworm segments or *Enterobius vermicularis* and occasionally an adult *Ascaris*. The other intestinal parasitic worms will have to be detected by finding the characteristic ova or, in *Strongyloides* infections, the larvae. If the ova are in abundance they will be observed by examining the stool directly under the microscope but if not, it will be necessary to resort to a concentration method.

A great number of these methods have been described and range from simple sedimentation in a conical glass to elaborate differential centrifugation in fluids of various specific gravities. There are at the present time two basic methods which appear to have advantage over other methods. The one is known as the zinc sulfate flotation method, already

described, and the other, acid-ether concentration. The latter is simple and yields excellent results. This test is performed as follows:

About 2 gm. of fecal material is emulsified with 10 c.c. of 15 per cent solution of hydrochloric acid. The material is filtered through two layers of gauze. This will result in the collection of about 8 c.c. of fluid which, after swirling, should be poured into a 15 c.c. centrifuge tube. To this is added 7 c.c. of ether and the mixture is vigorously shaken. It is then centrifuged for five minutes at a speed of about 1,500 r.p.m. All of the fluid, including the fatty plug, is poured off, the small sediment is obtained with a capillary pipet, placed on a slide with a coverglass and examined. Several authors (Hunter, Ingalls and Cohen) have advocated the addition of one of the wetting agents, such as Triton NE, and from their reports this would appear to be justified.

A number of special methods of examining for the presence of intestinal worms have been advocated. For example, biopsy of tissue from the rectum (Geih, Sher and Cheney) has been advocated as a method of diagnosing *Schistosoma mansoni*; also a flocculation test (Brandt and Finch) in which serum of the patient is used with an antigen prepared from adult worms and sensitized with lecithin, has been advocated in the same infection. A rectal scraper (Weller) for obtaining eggs of *Schistosoma mansoni* has also been devised. These same methods could be applied to the study of patients suspected of having *Schistosoma japonicum*. In cases in which an infection with *Schistosoma haematobium* is suspected the urine should be examined for ova and in cases of infection with *Paragonimus* the sputum should be examined. In examining sputum it is desirable to concentrate it by treating it first with dilute solution of sodium hydroxide and then centrifuging the specimen.

In order to test the importance of concentrating stools in the examination for ova, a series of 580 specimens were examined recently, first by the method of simple wet preparations on coverglass and then by concentration by the acid-ether method. The results are given in the tabulation.

TABULATION

COMPARISON BETWEEN ACID-ETHER CONCENTRATION AND NONCONCENTRATION METHODS IN EXAMINATION OF STOOLS FOR OVA OF INTESTINAL WORMS

	Specimens
Total examined.. . . .	580
Negative (both methods).. . . .	405
Positive (both methods, complete agreement).. . . .	43
Positive (both methods, incomplete agreement).. . . .	3
Positive (concentration) }	55
Negative (nonconcentration) }	
Negative (concentration) }	14
Positive (nonconcentration) }	
Times various types of ova were found (concentration).. . . .	123
Times various types of ova were found (nonconcentration)....	69

It becomes evident that ova were found almost twice as frequently by the concentration method as by the nonconcentration method. Most of these were *Trichuris trichiura* and hookworm ova which lend themselves particularly well to this type of concentration. Had the series contained

more cases of *Schistosoma* infection (Mathieson and Stoll) the ova in these cases also would have been found more frequently after concentration than otherwise. On the other hand since there is a strong tendency for *Ascaris* eggs to be lost by the concentration method, it is quite apparent that one should utilize both methods in order to make the maximal number of diagnoses.

SUMMARY

The clinical pathologist is the key figure in the diagnosis of tropical diseases. He should be thoroughly familiar with the various methods available for diagnosis and should remember that examination by the simpler methods yields satisfactory results; however, these methods require skill and experience and if he is to give satisfactory service to the patient, he must perfect himself in them. Repeated examinations are often necessary to establish a diagnosis. In the blood, bodily exudates and excreta there are a great number of objects that resemble parasites at different stages in their life histories. The clinical pathologist and the technician must always be on guard lest these objects be erroneously reported as animal parasites.

THE IMPORTANCE OF THE ISOLATION AND IDENTIFICATION OF TUBERCLE BACILLI*†

WILLIAM H. FELDMAN AND ALFRED G. KARLSON

The one unequivocal factor in the diagnosis of tuberculosis is the demonstration of the causative organism. Other procedures, while of significance, supply evidence that in the final analysis is only presumptive. Although tuberculosis in certain stages produces clinical signs so characteristic that the correct diagnosis is obvious, the picture is not complete without the demonstration of tubercle bacilli.

As the methods of screening tuberculous patients from the general population become more refined and patients with the earliest minimal lesions are detected, procedures for demonstrating the infective agent become more important. When the incidence of the disease recedes, laboratory means for its definite diagnosis will of necessity have to be resorted to with greater frequency. In addition, decisions of far-reaching importance concerning the safety to the community of the medically rehabilitated patients must be based on whether or not the patients continue to shed tubercle bacilli although the clinical signs suggest that the disease is arrested.

The medicolegal aspect of the problem must also be considered. Evidence of the true character of a tuberculous infection is more convincing in a court of law if the diagnosis is based squarely on the fact that tubercle

* The procedures mentioned are those used at the present time by the authors at the Institute of Experimental Medicine in the conduct of investigational studies.

† Abstract of paper published in full in the *Journal-Lancet*, 67:232-244 (June) 1947.

bacilli were demonstrated and definitely identified. Many diseases and conditions of obscure cause masquerade clinically as tuberculosis and their nontuberculous character is best established by methods designed to reveal tubercle bacilli if they are present

DEMONSTRATION OF TUBERCLE BACILLI IN INFECTED MATERIAL

For detecting tubercle bacilli in clinical material, the laboratorian has recourse to many procedures. Listed in order of their reliability the procedures are: (1) the animal-inoculation test, (2) cultural methods and (3) direct staining by the Ziehl-Neelsen method. We have had no experience with fluorescence microscopy and are not prepared to evaluate the method.

Cultural procedures for the detection of tubercle bacilli have reached a high degree of efficiency. However, more positive results will be obtained by the inoculation of guinea pigs than by cultural methods. Because of circumstances inherent in the materials submitted for examination, neither animal inoculation nor cultural attempts will yield as many positive results as are possible if suspected materials are used to inoculate both culture mediums and guinea pigs. Finally, it should be remembered that although one may properly question the identification of tubercle bacilli based on acid-fastness, cultural characteristics and other physical attributes, the results of animal-inoculation tests are usually unequivocal.

AN ADEQUATE ROUTINE FOR DEMONSTRATING TUBERCLE BACILLI

It might be proper to suggest what constitutes an adequate routine for demonstrating tubercle bacilli in material obtained from patients suspected of having active tuberculosis.

Assuming that the material to be examined is delivered to the laboratory in a satisfactory condition, the specimen should be subjected to the following procedures.

1. **Direct Smear Examination with Carbol Fuchsin Following Concentration if Necessary.**—No preparation should be considered free of acid-fast bacilli until it has been examined systematically for a period of ten minutes. Conversely, no specimen should be considered definitely positive if only one or two acid-fast bacilli are found.

2. **Cultural Methods.**—A medium of high efficacy should be chosen. A large-sized specimen should be provided if possible. The specimen should be concentrated by treating preliminary to culture with 3 per cent solution of sodium hydroxide or 5 per cent solution of oxalic acid. Cultures should be incubated for a minimum of eight weeks before being discarded as negative. The growth in "positive" tubes should be stained by the Ziehl-Neelsen technic and examined microscopically.

3. **The Inoculation of Guinea Pigs.**—Large guinea pigs weighing 1 pound (0.5 kg.) or more should be used. Two animals should be inoculated with each specimen. Animals of the same sex should be caged together. The suspected material should be injected subcutaneously, preferably suprasternally. Except in instances in which one animal dies as a result of sensitivity to a large dose of Old Tuberculin injected four weeks after inoculation, the animal should be killed for necropsy after eight weeks of observation.

4. Reporting Results.—Results of laboratory findings should be based entirely on objective observations. Consequently, results obtained by examination of direct smears should be reported either as "acid-fast bacilli found" or "no acid-fast bacilli found," as the case may be. It is entirely presumptuous for the laboratorian to report the presence of *Mycobacterium tuberculosis* on the basis of the presence of acid-fast bacilli in smears.

Cultures containing colonies of acid-fast bacilli should be reported as "growth typical of tubercle bacilli" or "no growth after eight weeks' incubation." If growth of acid-fast bacilli is obtained which is not typical, further studies including pathogenicity tests should be made before arriving at any conclusions.

Results of animal-inoculation procedures may be reported as "lesions of tuberculosis present" or "lesions of tuberculosis absent."

We would emphasize that the major responsibility for the diagnosis of tuberculosis rests squarely on the clinician. He should be thoroughly cognizant of the various laboratory means by which tubercle bacilli can be demonstrated, and should be familiar with the relative reliability and shortcomings of each. When material is submitted to the laboratory, the clinician should indicate how exhaustive the examination should be. If the search for tubercle bacilli is to include more than the routine examination of smears, the pathologist should be consulted concerning additional procedures.

SQUAMOUS CELL CARCINOMA IN SITU: HISTOPATHOLOGY AND CLINICAL DATA IN SIXTY-NINE CASES*

WILLIAM D. LOOSE AND JOHN R. McDONALD

Squamous cell carcinoma in situ is a specific disease entity and differs from ordinary penetrating squamous cell carcinoma in that it does not go beyond the confines of the epithelium from which it originated.

From the study of the data presented in the complete paper and a study of the literature on Paget's disease of the nipple, extramammary Paget's disease, Bowen's disease and intra-epidermal epithelioma it is concluded that all of these diseases conform to the histologic characteristics of squamous cell carcinoma in situ.

The average age of patients with squamous cell carcinoma in situ is generally that of the ordinary cancer-bearing age.

Squamous cell carcinoma in situ may exist for long periods of time as such without penetrating the boundaries of the epithelium which confine it.

From this study it is not known whether or not in situ squamous cell carcinomas, after varying periods of time, can penetrate the basement membrane and become invasive. However, it seems reasonable that this is possible.

* Abstract of paper submitted to *Surgery, Gynecology and Obstetrics*.

Multiple squamous cell carcinomas may be all in situ, or both penetrating squamous cell carcinoma and squamous cell carcinoma in situ may exist in the same patient at the same time.

The occurrence and removal of one squamous cell carcinoma in situ does not indicate that subsequent squamous cell carcinomas of the same location will be also in situ.

Squamous cell carcinoma in situ does not metastasize to the regional lymphatic nodes.

Five-year survivals for squamous cell carcinoma in situ are high. No patient in the group reported died as a result of squamous cell carcinoma in situ.

Squamous cell carcinoma in situ of the nipple bears a less favorable prognosis as it is associated with an adenocarcinoma in the depths of the breast. The prognosis then becomes the same as that for any other breast cancer.

All grades of malignancy of squamous cell carcinoma in situ may be found, but the grade of the malignancy is of histologic interest only. It bears no relation to the prognosis.

Squamous cell carcinoma in situ is often found associated with keratosis or leukoplakia.

In no case, except in those patients with squamous cell carcinoma in situ of the nipple, was there found an associated cancer of deeper-lying structures such as the sweat or sebaceous glands. It is concluded that squamous cell carcinoma in situ begins of itself within the cells of the squamous epithelium.

Wide local excision of a squamous cell carcinoma in situ is apparently adequate treatment. Extensive radical dissections, except in case of squamous cell carcinoma in situ of the nipple, and roentgen therapy as an adjunct seem unnecessary.

The term "precancerous" should be discarded. Either any given lesion is cancer or it is not cancer.

EXTRA-ABDOMINAL DESMOID TUMORS: THEIR DIFFERENTIAL DIAGNOSIS AND TREATMENT*

JAMES E. MUSGROVE AND JOHN R. McDONALD

Desmoid tumors are benign fibrous neoplasms, which have the peculiar characteristic of locally invading and destroying the adjacent striated muscle. They do not metastasize and there is no evidence, in the study reported in the complete paper, of a desmoid undergoing sarcomatous change.

Two theories of origin have been presented; namely, (1) that of a relationship to trauma and (2) that of an endocrinologic basis. Forty-one per cent of the thirty-four patients definitely linked the onset of the tumor with some previous trauma. However, only three of the thirty-four

* Abstract of paper published in full in the *Archives of Pathology*, (In press.)

tumors showed a trace of hemosiderin on microscopic examination. Thus, the histories tend to corroborate the traumatic etiologic basis while the microscopic findings tend to disprove it.

There is strong evidence that the endocrine glands may play a part in the origin and "physiology" of these tumors.

Desmoids are rare, but if the surgeon and the pathologist will keep them in mind, they will no doubt be found more frequently in the future than they have been in the past.

The extra-abdominal desmoid, like its counterpart in the abdominal wall, is found more often in the female, the ratio in this present series being 2.4:1.

In an attempt to differentiate between desmoid and low-grade fibrosarcoma, the following microscopic criteria are important: (1) Encapsulation: A well-circumscribed, encapsulated fibrogenic tumor should be considered malignant until proved otherwise. (2) Cellularity: An acellular fibrous tumor will usually be benign, while a high degree of cellularity definitely points toward malignancy. (3) Mitotic figures: Fibrogenic tumors not showing mitotic figures are benign, while those with numerous mitotic figures are malignant. However, tumors showing infrequent mitotic figures cannot be placed in either the benign or malignant class on the basis of this characteristic alone. (4) Pathologic mitotic figures: Finding one or more pathologic mitotic figures indicates malignancy. (5) Tumor giant cells: These cells are found only in the malignant fibrogenic lesions. (6) Cellular variation in size, shape, staining and nucleoli: As the cellular variation in these features increases so does the tendency toward malignancy.

When not all possible, desmoid tumors should be treated by radical excision. It is doubtful whether roentgen rays and radium are of value in treating desmoids, but when this form of therapy is used, it should be given in intensive doses.

Endocrine therapy holds out a ray of hope in the inoperable cases, but there is much to be learned about this form of therapy.

The rate of recurrence in the thirty-four extra-abdominal desmoids under review was very high, calling for a reassessment of the surgical and irradiation forms of therapy and for more research in, and clinical trial of endocrine therapy.

SALMONELLOSIS: EXPERIENCES IN MILITARY AND CIVILIAN PRACTICE*

LUCIAN A. SMITH

Because of the many guises in which salmonellosis masquerades, it is important for this condition to be considered in the differential diagnosis of fevers of undetermined origin, of acute and chronic enterocolitis and of those conditions which may be seen as complications of salmonellosis

* Abridgment of paper published in full in *Gastroenterology*, 9 351-356 (Nov.) 1947.

Increased recognition of the variegated manifestations of the disease will lead to an increase in the frequency of its diagnosis.

Observations were made on thirty-six patients seen in an army station hospital in New Guinea and in Luzon, Philippine Islands, and on four patients at the Mayo Clinic. There were seven infections with *Salmonella paratyphi A*, twenty-five with *Salmonella paratyphi B* (*schottmülleri*) and eight with *Salmonella* strains of group C. The *Salmonella* strains of group C encountered in the military service were identified by the Nineteenth General Laboratory of the United States Army. In the civilians, identification was made by the Minnesota Department of Health. Hospitalization was not required for perhaps thirty suspected patients in the army and for eleven civilians, and observations on these are not available. No deaths occurred in any of the patients seen.

The fact that salmonellosis is primarily a septicemia explains the necropsy findings of mesenteric adenitis, splenic and hepatic changes and occasionally metastatic abscesses. Gastro-intestinal changes are seen chiefly as hyperplasia, edema and shallow ulceration of Peyer's patches and sometimes of the lymph follicles of the colon. Injection of the blood vessels and thickening of the terminal part of the ileum and of the cecum are important when present.

The symptoms of salmonellosis correspond roughly with the organism involved. Group A organisms commonly give rise to so-called *Salmonella* fever, essentially a septic process with chills, spikes of fever, headache, sweating, nausea and vomiting without diarrhea. Group B organisms are most frequently associated with a brief febrile course combined with diarrhea or dysentery and periumbilical cramps. Group C organisms often lead to a septicopyemic course.

The physical findings in acute cases may be negligible or may include fever, tenderness of the edge of the liver, localized tenderness over the cecum, rebound tenderness of the lower part of the abdomen and, in less than 10 per cent of cases, enlargement of the spleen.

Five points about salmonellosis deserve consideration. The first is concerned with diagnosis. All who have studied salmonellosis will concede that the diagnosis is essentially a Laboratory one, with reliance on blood cultures, cultures of stools, urine or bile, and on the blood agglutination tests. Mention should be made, though, of the value of proctosigmoidoscopic examinations in acute salmonellosis. Proctoscopic studies of acute bacillary dysentery due to shigellosis show that the mucosa of the bowel even within two hours after the onset of symptoms may show certain diagnostic characteristics. These include diffuse edema and red hyperemia, mucosal hemorrhages of splinter or ecchymotic size, tiny pinhead-sized mucosal abscesses, exudate forming a pseudomembrane, and perhaps widely distributed shallow irregular ulcers. I have never seen this picture in cases of acute salmonellosis except in one patient who also had acute shigellosis. The proctoscopic examination in acute enterocolitis has, then, great negative value in excluding acute shigellosis. It has a positive value in a few cases of salmonellosis in which certain findings are suggestive of the diagnosis. These findings are a diffuse pink velvety edema of the mucosa with obliteration of the normal vascular markings, hyperplasia of the submucosal lymphoid follicles and sometimes small oval shallow ulcers

sitting on the surface of the follicles with very little evidence of mucosal reaction.

The second point concerns complications. Those encountered in this group of patients are shown in the tabulation. The only significant compli-

TABULATION
MANIFESTATIONS OF ACUTE SALMONELLOSIS IN FORTY CASES

Cases	Causative organism	Clinical diagnosis	Times made	Complications and associated conditions	Times occurring
7	<i>Salmonella paratyphi A</i>	<i>Salmonella</i> fever	5	Scurvy	1
		Enteritis, chronic	1	Urticaria	1
		Enteritis, acute	1		
25	<i>Salmonella paratyphi B</i>	Enteritis	22	Pericarditis	1
		<i>Salmonella</i> fever	3	Cholecystitis	2
				Malaria	1
				Shigellosis, acute	1
				Amebiasis, chronic	1
8	Unclassified	Enteritis, acute	1	Generalized peritonitis	1
	Unclassified	<i>Salmonella</i> fever	1	Acute arthritis of hip	1
	<i>Salmonella thompson</i>	Septicopyemic <i>Salmonella</i> fever	1	Jaundice and suppurative arthritis of knee	1
	<i>Salmonella hirschfeldii</i>	Ulcerative enteritis	1	None	
	<i>Salmonella oranienburg</i>	<i>Salmonella</i> fever	1	None	
	<i>Salmonella oranienburg</i>	Enteritis, acute	2	Localized peritonitis	1
	<i>Salmonella oranienburg</i>	Ileitis and cecitis, acute	1	Appendectomy	1

cation in *Salmonella paratyphi A* infections was the occurrence of symptomatic purpura and scurvy in an army officer who had been ill for two weeks in a forward area before he was evacuated to the station hospital. Administration of ascorbic acid led to prompt disappearance of the purpura and the gingivitis. In one patient with *Salmonella paratyphi B* (schottmülleri) infection, acute pericarditis developed two weeks after the onset of acute enterocolitis. The organisms of group C produced the most threatening complications. Generalized peritonitis occurred in one patient, with recovery on conservative treatment. Another patient was admitted with jaundice, a spiking fever and acute arthritis of one knee. Culture of his urine first revealed a *Salmonella* organism and on culture of the fluid from the knee joint this organism was found to be *Salmonella thompson*. The other patient with acute salmonellosis and acute arthritis of the

right hip did not undergo aspiration of the joint. One civilian with dysentery, blood in the stools, vomiting, and chills and fever off and on for ten days had marked rebound tenderness of the lower part of the abdomen. His infection was due to *Salmonella oranienburg*.

A third consideration is the fact that the surgical aspects should be emphasized because of cases in which generalized and localized peritonitis occur and because of the cases in which the findings simulate those of appendicitis. In the service, two patients not included in this series who had acute superficially ulcerative enterocolitis, as visualized on proctoscopic examination, also had obstructive appendicitis proved at operation. Two other patients, who were thought to have acute appendicitis, had acute ileitis probably due to acute salmonellosis. One civilian with pain in the lower part of the abdomen and tenderness in the right lower quadrant underwent appendectomy, at which time intense injection and velvety thickening of the cecum and terminal part of the ileum were also present. His first diarrhea developed after operation and for seven days he had a typical febrile course. Stool cultures showed *Salmonella oranienburg*.

The fourth point is the question of whether chronic diarrhea may arise as a result of acute salmonellosis. Bowel complaints and a tendency to diarrhea and anorexia continued for a week to a month in 60 per cent of the patients with acute enteritis in spite of treatment, the relief of fever and the disappearance of *Salmonella* organisms from the stools. If the form of acute salmonellosis which is associated with enteritis is not treated, I believe it may be a source of chronic diarrhea.

The fifth point concerns treatment. This is not too satisfactory and, because of the natural course of the disease, results are difficult to evaluate. Sulfaguanidine, bismuth, paregoric and tincture of iodine were tried in the first cases but without effect. Sulfadiazine, given three days in amounts usually entirely adequate to control shigellosis, ameliorated the symptoms and stool cultures became negative only to be followed by relapse when chemotherapy was discontinued. Best results were obtained with sulfadiazine in doses of 4.0 gm. initially, 2.0 gm. every four hours for four doses, 1.0 gm. every four hours for four doses and then 1.0 gm. every six hours for seven to twelve days of treatment. Vomiting occasionally made it necessary to give the initial doses intravenously. When fever was present, two days usually elapsed before a definite fall of temperature occurred.

In acute bacillary dysentery due to shigellosis, diagnosis may be made by proctoscopic examination within as little as two hours after the onset of the symptoms. If sulfadiazine therapy is begun within the first twenty-four hours after the onset of symptoms, my experience has been that the patient could be promised cessation of his dysentery by the next day. This dramatic response does not occur in acute salmonellosis and, although the patients feel more comfortable on treatment, those with enteritis usually continue to have loose stools for a number of days to several weeks. Disappearance of *Salmonella* organisms from the stools during sulfadiazine treatment occurs slowly and positive cultures are likely to recur if treatment is not continued long enough.

THE DIAGNOSIS OF HISTOPLASMOSIS IN ULCERATIVE DISEASE OF THE MOUTH AND PHARYNX*

LYLE A. WEED AND EDITH M. PARKHILL

The clinical manifestations of histoplasmosis vary extensively and may appear as ulcerated or indurated lesions of the oral cavity simulating those of tuberculosis, malignant disease and leishmaniasis.

Biopsy specimens may contain the organisms in sufficient numbers to warrant a diagnosis on histologic examination or the organisms may be so scarce as to render an etiologic evaluation impossible.

The organism "*Histoplasma capsulatum*," when present in biopsy specimens, may be easily isolated by inoculating the emulsified tissue onto blood agar containing 50 units each of penicillin and streptomycin per cubic centimeter of medium to inhibit bacterial growth. This is a suitable medium for other mycotic agents such as *Blastomyces dermatitidis*, *Coccidioides immitis*, *Cryptococcus hominis* and others.

Biopsy specimens should be handled so that adequate material may be held separately for suitable bacteriologic investigation if the histologic examination does not reveal a neoplastic process.

MEDICINE IN AVIATION†

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Medicine in aviation may be applied to two groups: the air crew and the passenger. Factors which may be of great importance in air crew members may have no significance in passengers. As has been mentioned in a previous article, on ascending to altitude certain physical changes which affect the body physiology occur; namely, lowered barometric pressure with resultant decreased oxygen tension and expansion of body gases, changes due to motion, such as acceleration and deceleration, and cold. A further change is the individual emotional response to transportation by air. Because of these changes it is important to consider carefully two groups of aviation subjects; namely, the air crew and the ill patient to be transported by air. The matter of transportation of the ill patient has been emphasized by Grant, Hippke, and Tillisch and his co-workers. The indications and contraindications for the aerial transportation of ill patients are not necessarily applicable to the casual air passenger.

The determination of the status of the cardiovascular system is of importance for both pilot and passenger. A hypersensitive carotid reflex has been shown by Tillisch and Lovelace to be of great importance in the pilot for the reason that it may cause sudden unconsciousness. Therefore a pilot with this condition should be disqualified. The presence of

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postural hypotension in a pilot is disqualifying for a similar reason as pointed out by McFarland and his co-workers. At present the most commonly accepted method of examining for postural hypotension is to have the examinee rest in a supine position until a basal blood pressure and pulse rate are obtained. The examinee then stands erect for three minutes and the blood pressure and pulse rate are again taken. If a significant fall in blood pressure and rise in pulse rate occur or if the examinee evinces any signs of unconsciousness a diagnosis of postural hypotension is made. Evidence of signs of unconsciousness is of more importance than the finding of a fall in blood pressure alone. In the examination for postural hypotension it is also helpful to elicit any history of unconsciousness occurring on rising from a supine position. In passengers neither a hyper-sensitive carotid sinus reflex nor a postural hypotension contraindicates flying.

Valvular heart disease or hypertension has always been considered a contraindication for flying a plane. This question has not been finally settled. Although there has never been a satisfactory statistical analysis to determine the incidence of sudden unconsciousness in patients who have valvular heart disease or hypertension, it is suspected that it would be very little higher in these patients than in a control group. Yet the chief reason for considering these two conditions contraindications for piloting a plane is the supposed increased likelihood of sudden unconsciousness or weakness. A person with severe hypertension or severe valvular heart disease should not fly a plane. In addition a person with cardiac decompensation caused by either of these two conditions or by any other condition had best fly as a passenger only when absolutely necessary and when there is adequate oxygen available. A person with cardiac decompensation already has anoxia and the added load of the anoxia of altitude on an already impaired circulatory system may have harmful effects. The nervous tension associated with flying may further aggravate the cardiac condition. In the final analysis a person with mild uncomplicated hypertension or well-compensated valvular heart disease can probably pilot a plane with safety. One who has moderately severe hypertension or valvular heart disease with even minimal cardiac decompensation had best not fly a plane. The passenger with either hypertension or valvular heart disease can be transported safely by plane unless he has severe hypertension with a history of the complications of hypertension or unless he has frankly decompensated valvular heart disease; in these latter events the passenger had best not fly. If it is necessary for these patients to fly, oxygen should be administered to them from the ground up.

The role of coronary heart disease in aviation has been emphasized by Benson, Graybiel and McFarland, and White. This condition is of a more serious nature in the pilot than the aforementioned types of heart disease because of the suddenness and severity of the attacks. Evidence of coronary disease in a pilot should contraindicate flying by that person. Coronary heart disease in the passenger must be handled as an individual problem. It is best not to fly for a considerable period of time after myocardial infarction. A person with easily induced anginal attacks had best not fly. The patient who may have marked apprehension to flying which aggravates his coronary disease had best not fly. A trip by plane that necessi-

tates going to higher than normal altitudes should be contraindicated for a person with coronary disease. Generally the patient who has severe coronary disease should be advised not to fly unless other forms of transportation would put even a greater strain on the heart; if he does fly, oxygen should be administered at any altitude above 7,000 feet and a mild sedative prescribed to allay any nervous tension.

Diseases of the respiratory system vary in their role as contraindications to flying. The common cold, sore throat and sinusitis all may increase susceptibility to aero-otitis and otosinusitis. The application of the usual vasoconstrictor drugs, such as amphetamine (benzedrine) or 2-aminoheptane sulfate (tuamine), may shrink the tissues in the nasopharynx and nasal cavity so that the middle ear or accessory sinuses can be adequately ventilated. Bronchitis, bronchiectasis, pneumoconiosis, pulmonary abscess and bronchogenic carcinoma are not in themselves contraindications to the patient's flying as a passenger unless such conditions are sufficiently severe as to cause respiratory embarrassment. In the latter event these persons should not fly unless oxygen is available and is used. Patients suffering from pneumonia also should be given oxygen when flying even though no evidence of respiratory impairment is present. This is done for the reason that the patient with pneumonia already has endogenous anoxic anoxia and the addition of even a further slight anoxic anoxia as a result of his going to altitude may be sufficient to cause the patient grave trouble. The advisability of flying on the part of a patient with active pulmonary tuberculosis is in question; certainly if the lesion is more than minimal the patient should not fly. The most important factor in a tuberculous patient's flying is whether or not he has a pneumothorax. The dangers to a patient with pneumothorax in traveling by air are numerous. Rapid contraction and expansion of the collapsed lung are deleterious to the healing process of tuberculosis. Tearing of adhesions attached to diseased pulmonary tissue may result in hemorrhage or in seeding the pneumothorax cavity with tubercle bacilli. Excessive compression of the lung may reduce the vital capacity seriously. Dowd reported the death of a patient with pneumothorax occurring as a result of transportation by plane at an altitude of 16,000 feet.

Persons with asthma should not travel by air during an acute attack and those suffering from frequent severe attacks should not fly. The person with mild asthma may fly between attacks without difficulty.

Gastro-intestinal ailments in crew members vary in importance according to the type of disease. Peptic ulcer, the most common chronic gastro-intestinal disease found in pilots, varies in its importance according to the severity of the lesion. A pilot who has an acute peptic ulcer with pain and who is threatened with perforation or hemorrhage should not fly a plane. A pilot who has a healed or a chronic ulcer without symptoms may be able to fly without too great a risk. Certainly a pilot with any evidence of ulcer should be kept under observation for a time to determine the degree of severity of the lesion before being allowed to fly. A passenger with peptic ulcer can be transported with minimal risk except in a case of threatened perforation. In this case, if the patient must be transported by plane, he should be flown at a low altitude to obviate the danger of increased intragastric and intra-intestinal pressure due to the expansion

of gases at increased altitudes. With the use of pressurized cabins in planes this danger will be entirely removed.

Gallbladder disease in a pilot should contraindicate his flying because of the danger that sudden acute colic might render him incapable of flying a plane. Gallbladder disease in a passenger in no way should interfere with plane travel any more than with any other form of travel. The severity of chronic diseases of the small and large intestine in the pilot will determine his ability or inability to fly. In the passenger these diseases are usually of little consequence in determining that person's risk in flying. A disease that is frequently overlooked and yet may be of very serious import in flying is acute gastro-enteritis in the pilot. The reasons this disease is of importance in the pilot are its frequent occurrence and at times its acute debilitating effect which may so weaken the patient that he is incapable of carrying on his duties as a pilot. There have been incidents reported in which a pilot has been suddenly prostrated by acute gastro-enteritis with severe vomiting and diarrhea. The sudden exacerbation of the disease when the pilot is in a plane may be explained by the hyperirritability of the gastro-intestinal tract induced by motion of the plane and the expansion of gastro-intestinal gases which occurs at altitude. For the passenger this group of diseases is of little significance in so far as determining the ability to fly is concerned.

Genito-urinary diseases do not play an important part in aviation either from the standpoint of the pilot or the passenger unless they are severe. A renal or ureteral calculus is always a potential danger in a pilot because of the possibility of sudden severe colic and collapse. Gonorrhea in itself is no contraindication to a pilot's flying unless his general physical condition is so seriously impaired that he cannot carry out properly his duties in flying or unless the treatment for the disease might interfere with proper flying.

Active syphilis is adequate cause for suspending a pilot from flying until the clinical signs and symptoms have disappeared and until the patient is noninfectious and has been adequately adjusted to the disease and treatment. With the advances in the treatment of syphilis which have resulted from the use of penicillin and from more rapid treatment with the arsenicals and bismuth, these requirements can be usually met in four to six weeks. It must be emphasized that the serologic test for syphilis is not considered a test of efficacy of treatment or degree of activity of the disease except in early syphilis. Therefore, providing the patient has been adequately treated and there is no evidence of active syphilis, the results of the serologic tests may be ignored in determining the qualification of the person for flying. Syphilis in a passenger does not contraindicate flying unless the disease is in an infectious stage.

Diabetes mellitus of even mild degree occurring in a pilot should be cause for permanent grounding because of the dangers of diabetic coma and hypoglycemic reaction. Observations on passengers with diabetes mellitus have revealed no serious effects from flying. Hyperinsulinism from any cause is a definite danger when it occurs in a pilot. Hyperthyroidism or hypothyroidism of such a degree as to be clinically evident is a contraindication for a career of flying; either disease in a passenger in no way should interfere with his flying.

Diseases of the skeletal system, such as various types of arthritis, residuals of poliomyelitis and fracture deformities, are to be judged solely by the amount of mechanical interference present in the person handling the controls of a plane.

The aerial transportation of patients who have intracranial injuries was accomplished by the armed services without adverse effect. In order to combat the anoxia of brain tissue associated with increased intracranial pressure, oxygen should be administered from the ground up during flight. Encephalography or ventriculography within the past seven days or any condition in which intracranial entrapment of air is demonstrated is a contraindication to travel by air.

The psychotic patient should not be transported by air because of the difficulty in controlling him on a plane and because of the potential danger that he may get out of control and do damage to the ship and crew. There is no contraindication for the psychoneurotic patient's flying except that these patients are usually more prone than usual to suffer from airsickness.

The patient with severe anemia is already suffering from an anemic anoxia. If that patient is taken to high altitudes, there is superimposed an anoxic anoxia and the patient may evidence clinical signs of anoxia. Thus, the severely anemic patient should receive oxygen on flying to prevent this complication. The slightly anemic patient can usually be transported by air without difficulty because the anemic anoxia is so small.

SUMMARY

The technical advances in aircraft are lessening the number of medical contraindications for flying. The increased efficiency of oxygen systems and the increasingly extensive use of such systems has made it safer now than formerly for the patient with hypoxia to fly. This includes the patients who have respiratory illnesses, severe or complicated cardiac disease and anemia. The use of pressurized cabins in aircraft will obviate the precautions now necessary in transporting patients who are suffering from conditions that would be made worse by the expansion of intra-abdominal or intrathoracic gas which occurs in unpressurized aircraft. Also as people become increasingly accustomed to transportation by air and as such transportation becomes increasingly safe, there will be a decrease in apprehension and thus in nervous stimulation, with its side effects, for the individual in flying.

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